ALLERGY: STRANGEST OF ALL MALADIES

A POPULAR STUDY OF THE CAUSES AND METHODS OF TREATING ASTHMA, HAY FEVER, URTICARIA AND OTHER ALLERGIC DISEASES

Under the title of *The American Association for the Advancement of Science Series* this book was published in the U.S.A. as *Strange Malady.*

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Yet one caution let me give, by the way, to my present or my future reader who is actually melancholy, that he read not the symptoms or prognostics in this following tract, lest by applying that which he reads to himself, aggravating appropriating things generally spoken, to his own person (as melancholy men for the most part do), he trouble or hurt himself and get, in conclusion, more harm than good.

ROBERT BURTON—*Democritus to the Reader.*

NOT A SURREALIST'S DREAM BUT JUST A FEW OF THE IDIOTIC, UNRELATED THINGS TO WHICH ONE MAY BE ALLERGIC

ALLERGY:

STRANGEST OF ALL MALADIES

By
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With a Frontispiece by Leslie Gill
and 22 Line Drawings by John P. Tillery

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TO

MY WIFE

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FOREWORD

OUT OF A WIDE EXPERIENCE AS A DISTINGUISHED SPECIALIST WHO has written standard texts for other experts in his field, Dr. Vaughan has prepared for non-technical readers a comprehensive treatise on allergic diseases, covering their history, origin, nature, diagnosis, treatment and other phases of the subject, in a facile style as pleasant and easy to read as the pages of a popular novel. Competent exposition of scientific fact and charm of presentation are rarely so well combined as in his latest book, *Allergy : Strangest of all Maladies.*

The new volume is the second of the Advancement of Science Series of non-technical books on science, which are published by Hutchinson's Scientific and Technical Publications. Dr. Vaughan's book deals with those curious ailments of man and animals that are due to some form of special sensitization and set in motion by unwitting contact with the substance to which the body is sensitive. Among the common allergic diseases are hay fever, hives, ivy poisoning and 'sick headache.' Since these diseases seem to have little in common, it is not surprising that their similarity in one essential respect was long overlooked.

So diverse are the manifestations of allergic reaction that investigators of the different ailments in the allergic group have had difficulty in settling on a common word for designating them. One that has found much favour is atopy, from the Greek word ἀτοπία, meaning literally 'out-of-the-wayness' or simply strangeness, from which Dr. Vaughan has taken his title. Dr. Arthur Coca, of New York, a pioneer in the study of allergic diseases, on the suggestion of his friend, the late Dr. Edward D. Perry, professor of Greek at Columbia University, first used the word atopy to designate diseases like hay fever and asthma. Classical Greek writers employed the word frequently, obviously not for allergy, about which they knew nothing, but for strangeness or even absurdity in a general sense in any kind of experience, including disease.

The general reader of *Allergy* will certainly be surprised at the variety of affections now considered by allergists to be the results of special sensitiveness of the body to some particular substance. It is equally certain that many physicians will be startled at the interpretation of phenomena they have long considered to be due to other causes. The majority of the medical profession are prepared to accept hay fever, asthma and hives as examples of distressing responses in patients unfortunately sensitive to ragweed pollen or

strawberries or shrimps, and the role of allergy in chronic diseases like tuberculosis is familiar, but it will be sudden news to many practising physicians that drowning and certain acute physical consequences of unrequited affection might, under some circumstances, be of allergic origin. These are days when the 'lay' public often reads popular medicine more regularly than the doctor reads his technical journals, and many a physician nowadays is at least surprised, if not nettled, to have a patient explain some recent advance in medicine to him. It is, after all, not a bad sign of the times, as long as the sources of the popular information are good, as in the present instance.

The problems of allergy are as complicated as any in medicine. Light is barely dawning in their understanding. Dr. Vaughan is candid in exposing the questions vexing the most learned in his specialty and the confusion achieved at best in assembling information to portray 'the crazy pattern of the allergic picture,' as he himself terms it. A less understanding expert might have capitalized on his special knowledge with *ex cathedra* presentation. Dr. Vaughan's approach to his audience has none of this flavour ; it is friendly, humorous without flippancy, and serious without burdening the reader. Allergy is one of medicine's great puzzles. In many patients it is only a nuisance ; in others it is of deadly import. The public should know more of it, on the simple theory that forewarned is forearmed. *Allergy* furnishes a good understanding in an engaging manner.

ESMOND R. LONG, M.D

CONTENTS

Part Four

ALLERGENS

Part Five

MAN AND HIS ALLERGY

LIST OF ILLUSTRATIONS

Half-tones

Line Drawings

PART ONE

AT THE BEGINNING ALLERGY WAS UNKNOWN

Chapter I

THE STRANGENESS OF OLD ACQUAINTANCES

CAROLINE'S MOTHER HAD COOKED A NEW KIND OF BREAKFAST CEREAL. Caroline thought she would enjoy it. She placed a spoonful in her mouth.

The result was as unexpected as it was terrifying. Almost at once her lips and tongue swelled to double their normal size, she had a violent fit of coughing, and it seemed to her that she was suffocating. The back of her throat swelled, and Caroline lost consciousness. Her mother, frantic with fear, called the doctor who lived next door.

Dr. Smith, quickly realizing the situation, muttered something about "Allergic shock with angioneurotic œdema," while opening his bag. In a jiffy he filled his syringe with adrenalin and injected it into Caroline's arm. Several injections were needed before she was quite all right again, but by early afternoon she was playing around the house as though nothing had happened.

Caroline's mother couldn't understand it, especially when Dr. Smith said that the swelling had probably saved her daughter's life. It had started so quickly that she could not swallow the cereal. If she had done so she would probably have died from allergic shock !

What manner of strange disease could this be that possessed the power to kill almost in a moment and yet left no trace of its presence a few hours after a nearly fatal attack ?

The doctor told Caroline to come to his office the next day so that she could be skin-tested. She didn't know just what he meant, although he explained that solutions of the foods and other things that might be suspected of causing such attacks would be rubbed into scratches made on the skin or injected through a hypodermic needle.

Skin Tests

Tests for allergy ! This sounded exciting to Caroline, who had never taken tests except in school. She was still more excited when

a nurse brought in a shiny metal tray filled with syringes which Dr. Smith filled from a row of little rubber-stoppered bottles. When the first needle went into her skin Caroline said "Ouch !" It didn't hurt much, though, so she let the doctor prick her back with needle after needle.

When the tests were completed, Dr. Smith pointed to one which had swelled like a bee sting and which he said was 'positive.' This reaction showed that Caroline was allergic or sensitized to flax seed. There was flax seed in the new cereal.

To the mother's exclamation that manufacturers should not be allowed to use such poisonous things, the doctor explained that there is no objection to flax seed in breakfast foods. It is a perfectly good food, and most people can eat it without unpleasant symptoms. The trouble wasn't with the food. The trouble was with Caroline. She was allergic to it.

Flax seed has gone somewhat out of style as a food, not because it is poisonous, but because we have other foods which most people like better. In the days of Julius Cæsar flax seed meal was so widely used as a porridge that it might have been called the Roman breakfast food. You or I might eat it without harmful effects, but Caroline couldn't.

Dr. Smith explained that there are ways in which Caroline might be exposed to flax seed other than by eating it. "Never use a flax seed poultice on her, no matter what doctor may advise it. Don't forget that linseed oil is flax seed oil. Therefore, she might develop symptoms such as hives[1] or asthma when she is near fresh paint or varnish. Linen comes from flax, but we have not found that persons allergic to flax seed must necessarily avoid the flax fibres in linen cloth."

Atopy—A New Name for an Old-timer

"Allergy is a very queer disease," the doctor explained. "In fact, another word for it is atopy,[2] which, derived from the Greek, means strange disease. It's not strange in the sense of rarity—only in the sense of being different from other common maladies, such as the bacterial infections, heart disease, diabetes, ulcer, and the like.

"As a matter of fact, recent surveys indicate that from 7 to 10 per cent of the population have the disease with such severity that sooner or later they must consult a doctor. Imagine, one out of ten people ! Worse than that, the surveys indicate that about half the population becomes allergic to some substance at one time or another in their lives."

[1] In America the word 'hives' is extensively used to cover a variety of skin eruptions attributed to personal intolerance to various offending substances or experiences. In English parlance the word 'urticaria' is its nearest equivalent, but the more popular usage of the word is 'nettle rash.' The true meaning of hives, however, will be apparent in the text.

[2] This name was proposed by Dr. Arthur Coca of New York, a leading immunologist.

Caroline's mother still didn't understand how, if allergy is not an infection and the cereal wasn't really poisonous, Caroline could have contracted the disease. No one in the family had ever had anything like it.

"Possibly not," said the doctor, "but the disease is supposed to be hereditary. Caroline's reaction was unusually violent, and I should not expect other members of your family to be affected in the same way. If Caroline inherited the disease she didn't inherit allergy to flax seed. What she received from her ancestors was a tendency—the tendency or predisposition to become allergic to some substance to which she may be exposed. Hers is a case of food allergy. She might have become allergic to things she breathed instead of what she ate. Hay fever is an allergic disease caused by the pollens of trees, flowers, grasses, and weeds."

Her mother then recalled that she herself had had hay fever since adolescence.

"Yes, and there are other allergic diseases besides food idiosyncrasy and hay fever. The common allergic diseases include hay fever, asthma, hives or nettle rash, some forms of eczema, and some cases of chronic headache, especially the type that comes and goes. Migraine or sick headache is often allergic. Then there are a lot of people with indigestion due to allergy but erroneously ascribed to some other cause, especially so-called chronic appendicitis. Serum sickness is an allergic disease. There are other ailments in which allergy plays a more or less important part."

A Common Illness

Dr. Smith did not exaggerate the importance of allergy. There are probably 6,000,000 hay fever sufferers in the United States. Imagine New York with everybody sneezing at once! Estimates as to the number of asthmatics in the United States range from 600,000 to 3,500,000. Visualize Boston or Chicago with everyone huffing and puffing. There are probably over 3,000,000 with recurrent sick headaches and 4,000,000 who suffer more or less intermittently or continuously from hives. Nearly 4,000,000 have some form of indigestion due to allergic causes. The present estimate of 600,000 with allergic eczema, or dermatitis, may well be multiplied by ten when we include allergic occupational skin diseases.

These figures are necessarily approximate since it would be out of the question to make a complete census of all persons. They are, however, based upon population surveys of groups varying in number from 500 to 7,000, covering such widely scattered but representative areas as Massachusetts, New York, Virginia, Michigan, Louisiana, Colorado, Nevado, and California, and upon information for the country as a whole, gathered from World War draft-board examinations, morbidity statistics of the army during the war and life-insurance statistics. In the case of hay fever, for example, the

per cent of population affected ranges in the different surveys from three, on the Eastern Seaboard, to ten in localities in the Mississippi drainage area. In this latter area ragweed grows more abundantly than elsewhere. We might speak of it as the great ragweed hothouse. Not only does the frequency of hay fever in a given community vary with the abundance of the causative agents, but it varies also with the type of person living there. American Indians suffer from hay fever, but are notably less susceptible to the disease than the white man. The frequency among Negroes is about one-third of that among whites. A five per cent estimate, totalling 6,000,000 sneezers, leans toward the conservative side.

In 1925 veterans' compensation for service-connected disability due to asthma amounted to $2,874,204. Life-insurance statisticians estimate that asthma causes the loss of 13,000,000 workdays each year.

There are probably 12,000,000 persons in America who at one time or another will be sufficiently ill from one or more of the allergic diseases to require medical care. There are probably in the neighbourhood of 60,000,000 who will experience some mild allergic symptom at some time during their lives.

One of the surveys, comprising 3,000 persons in 1,000 families, showed that 45 per cent of the families had one or more cases of allergic disease. Thus allergy strikes close to home for all of us.

The Allergic Diseases

Hay fever, *asthma*, *urticaria* (*hives*), *eczema*, *ivy poisoning* and *migraine headaches* are the commoner allergic diseases. There are no statistics on the frequency of the more unusual allergies. Some are so rare that only a physician or one who has had the disease would recognize them by name. The names themselves are at times quite formidable.

Angioneurotic œdema, less frequently called acute circumscribed œdema, consists of intermittent attacks of swelling of the tissues under the skin. The face is often involved. One may awaken with an eye swollen shut or a lip that is two or three times its normal size. Any area of the body may be involved. The condition even affects internal structures, in which case the symptoms are difficult to diagnose because they may suggest some other internal disease. After a few hours or a day or two the swelling subsides, leaving no trace of its former presence. When the swelling commences immediately after the eating of some food, as it did in Caroline's case, the cause-and-effect relationship may be obvious. When it appears to develop spontaneously the cause may be hard to trace.

Agranulocytosis is pretty much of a word, but to make it more difficult there are several other names for the same disease. These include neutropenia, granulopenia, malignant neutropenia and agranulocytic angina. In agranulocytosis the protective white blood cells, the granulocytes or neutrophils, disappear almost entirely

from the blood, leaving the patient abnormally susceptible to infection. This is due in part to allergic sensitization to certain drugs such as aminopyrine, dinitrophenol, sulfanilamide and arsphenamine.

Periarteritis nodosa, fortunately rare, is a disease of the arteries, often accompanied by asthma.

Thromboangiitis obliterans is another circulatory disturbance in which clots form in the veins, interfering with the circulation and causing local tissue death and gangrene, especially in the extremities, the fingers and toes. There is evidence, as yet not completely proved, that allergy to tobacco is a factor in this disease.

Allergy to tobacco and to some foods, drugs and pollens has also been incriminated in some cases of *angina pectoris*.

There are two varieties of *purpura* in which food or drug allergy may be a causative factor. In purpura little black-and-blue marks, spontaneous hæmorrhages, appear in the skin or mucous membranes. They also occur internally, but the victim doesn't know of this because he cannot see them.

This about completes the tongue twisters, but doesn't finish the list of diseases in which allergy may play a part. In several conditions which are usually due to other causes an allergic factor may prevent successful treatment unless it also is controlled. They include recurrent *cold sores* or herpes ; *canker sores* in the mouth ; chronic *head colds ;* nasal *polyps ;* some cases of *sinusitis* ; chronic or recurrent *indigestion ; colic ; colitis ;* some cases of *gall bladder disease ; cyclic vomiting ; Ménière's disease* (recurrent severe attacks of dizziness) ; spastic *constipation* ; and some forms of chronic *bronchitis.* Food allergy may be the cause of chronic fatigue. Of course, there are other causes also.

Further discussion of the less common allergic diseases would carry us into technical matters beyond our present interest. Just now we want to know what allergy is, why it affects some persons and not others, what may be done to avoid it, and how we may be relieved if we happen to be victims of the disease.

Chapter II

HOW OLD IS ALLERGY?

THE HISTORY OF TYPHUS FEVER, CHOLERA, SMALLPOX, AND OTHER epidemic plagues epitomizes in some measure the history of the human race. Most of them have existed since the days of aboriginal man No doubt allergy has likewise been with us from prehistoric times, but its story has been less turbulent than that of the others because it is a disease of the individual rather than of groups. Not

being contagious, it doesn't become epidemic. Each victim must suffer alone, and since he is not dangerous to his neighbour, he arouses little interest among health officials or those other agencies created for the protection of the community. This is true, in spite of the fact that our strange malady affects more persons in North America than any other single disease.

The story of allergy can be followed through the centuries only by way of chance remarks here and there among the writings of early observers. The allergist, attempting to find first descriptions of the disease, must work like the archæologist who digs here and there in probable places, finding an occasional broken urn or fragmented tablet which tells him of the civilizations which existed in remote times.

One reason why there were few early descriptions of cases with allergic symptoms is that printing was not used until about the fifteenth century. Before then few people wrote, there were few copies of what they wrote, and most of these were eventually lost. Those who did write indulged in generalizations rather than specific instances. There were no case reports or descriptions of interesting isolated episodes such as we commonly see in the medical writings of to-day. Early physicians chronicled spectacular mass diseases such as epidemics. They were little interested in isolated instances of some curious illness which might, after all, be purely nervous or imaginary.

Food Idiosyncrasy

Fortunately there were a few who did mention such symptoms. As a consequence occasional records have been found, even from the time of Hippocrates, the earliest authoritative medical writer, who lived in the golden age of Pericles about 400 B.C. Hippocrates wrote of many things. Among them was cheese and its effects on man. This is what he said: '*To me it appears . . . that nobody would have sought for medicine at all, provided the same kinds of diet had suited with men in sickness as in good health. . . . For cheese does not prove equally injurious to all men, for there are some who can take it to satiety without being hurt by it in the least, but on the contrary it is wonderful the strength it imparts to those with whom it agrees; but there are some who do not bear it well, their constitutions are different, and they differ in this respect, that what in their body is incompatible with cheese is aroused and put in commotion by such a thing; and those in whose bodies such a humour happens to prevail in greater quantity and intensity are likely to suffer the more from it. But if cheese had been pernicious to the whole nature of man, it would have hurt all.*' To-day we realize that Hippocrates was describing food idiosyncrasy, which we now call food allergy.

To Lucretius, the Roman, is attributed one essay, no more, but it is the most famous contribution from the Rome of his generation. It was made public after his death by his good friend Cicero. No

writers of the time except Cicero seem to have known anything of Lucretius. Years ago some over-critical investigator raised the question whether Lucretius and Cicero were one and the same man. It was suggested that Cicero, having much to say that might sound too liberal, credited his own essays to his friend, knowing that a dead man could not be punished. Savants have since agreed that Lucretius wrote more learnedly than did Cicero and therefore probably really existed.

Lucretius said something about allergy. In *De Rerum Natura* (The Nature of Things) he started the adage, "what's one man's food is another man's poison." He didn't say precisely this. He wrote *Quod aliis cibus est aliis fuat acre venenum*, "What is food for some may be fierce poison for others."

He has since been quoted by many and his phrase has become a household word. He has been misquoted far oftener than not. Beaumont and Fletcher wrote in *Love's Cure* :

> What's one man's poison, signor,
> Is another's meat or drink.

Now Lucretius did not write that one man's food *is* another's poison. Instead he said that food for some *might* be poisonous for others. He thus showed himself a better observer, shall we say a better allergist, than those who have since translated his saying.

In those days and until recently, abnormal reactions to harmless foods were not called allergic but were spoken of as idiosyncrasies. Literally translated, this word carries much the same connotation. Idiosyncrasy implies a 'reaction peculiar to the individual.' Allergy implies an 'altered capacity to react.'

So we see that Hippocrates and Lucretius, two millenniums ago, recognized an abnormal response to the eating of certain foods.

Asthma

It seems probable that what we now call asthma existed in the time of Hippocrates. However, this first great physician used the term merely to indicate difficult breathing. Anyone who was 'panting' had asthma. It was not until 1607 that Van Helmont wrote of a type of difficult breathing which occurs in spasmodic attacks with intervening periods of freedom from symptoms, a condition which we recognize to-day as 'old-fashioned' bronchial asthma.

Hay Fever

Until recently there has been less agreement as to the antiquity of hay fever. People have spoken of it as a new disease. Have you ever wondered whether there is such a thing as a new disease?

Have all human maladies existed since the days of the cave man? Obviously not. There have been parasitic infections in certain animals which never bothered man until those animals

appeared in man's environment or were first used as food. Tuberculosis was unknown to the American Indian before the coming of the white man. True, it had been a disease of other humans elsewhere in the world. Undulant fever, which is now quite common in America, was originally limited to the Island of Malta, where the inhabitants contracted it from infected goats' milk. From there it spread to other areas bordering the Mediterranean Sea, whence it was brought to America in herds of imported goats. Like tuberculosis this disease, new to persons living in North America, has since become widespread.

Then there are truly new diseases, often man made. No cave-dweller suffered from mustard-gas poisoning, one of those diabolic inventions of man designed for the destruction of his own species. Many newly developed chemicals are poisonous. Some of those used as medicines turn out to be harmful for certain persons, creating a new malady different from that which they should cure. We shall see that allergy may play a part in such cases.

Did Hay Fever Originate in Modern Times?

In general we may say that most of the diseases described as new existed for some time before their first recognition. This is certainly the case with hay fever. Hay fever is a dated disease. We can go back to a very specific time prior to which there was, officially, no such thing.

Bostock's Catarrh, a 'New' Disease

In 1819 John Bostock, a famous London doctor, described a seasonal catarrhal affection of the nose which soon came to be known as Bostock's summer catarrh. Before then all sorts of acute and chronic nasal conditions were known by the general term 'catarrh.' For the first time in history this physician separated a distinct group from among those who were subject to colds and catarrhal affections. In this group symptoms occurred with great regularity and only in the summer. Presumably such cases had existed for an indefinite period, needing but differentiation from those with similar symptoms occurring without recognizable periodicity.

Bostock described this as a new disease and a rare one. He was a very learned man. He had been professor of physiology at the University of Liverpool and in 1819 held the same chair at the University of London. He had written widely and authoritatively, had even translated the works of Pliny, the great naturalist of ancient Rome. I have little doubt that he had a very large practice in London. Nevertheless he wrote that after nine years' search he had seen or heard of only twenty-eight persons afflicted with his new disease. There were ten other questionable cases. When we think of the millions with hay fever in America to-day we might

well conclude that the disease is on the increase, that it was rare in the days of Bostock and that it must have been a new disease at that time.

It might have been a much rarer disease a hundred years ago than it is now, but we cannot say that because it was first recognized in 1819 it was not a very old malady even then.

Evidence that Hay Fever is an Ancient Disease

Within recent years allergists have made community surveys, interrogating every member of certain population groups. There were no such surveys before fifteen or twenty years ago from which one could draw comparisons as to the commonness of the allergic diseases. About all we can find in the medical writings before the time of Bostock is the occasional description of unusual cases. Individual cases of sneezing or wheezing after exposure to roses or cats have been found in the medical literature even as early as the time of Galen, the great Roman physician who lived in the second century A.D. It is interesting that things which were said to cause attacks were those that could be easily recognized. The earliest clear descriptions of what to-day we call hay fever were written in 1565 by Botallus, a physician living in Padua, and in 1607 by Van Helmont, a Flemish doctor. Eleven accounts of seasonal hay fever or of hay fever with asthma, all dated before the year 1700, have been discovered. All but one described the symptom as due to roses, mentioning particularly the odour of roses. The one exception, that of Van Helmont, described attacks of asthma occurring only during the summer. We may infer that Van Helmont's case was more like the pollinosis of to-day, due to pollens of grasses or weeds or some other common plant, not brightly coloured and therefore unsuspected.

Undoubtedly there were more than eleven men who described the curious response to roses and other things before 1700, but much of the early writing has been lost, and this is all that patient investigators have so far unearthed.

Allergic Skin Diseases and Headache

Hippocrates wrote of hives, or urticaria, due to mosquito bites and accompanying stomach upsets. The term eczema, like leprosy, was used so indiscriminately that it was not until early in the nineteenth century that any serious attempt was made to separate this from a large number of other chronic skin diseases. Angioneurotic œdema, recurring swelling of the soft parts of the skin, particularly of the face or hands, was first described in 1778, but there is no evidence that it was a new disease at that time.

Paroxysmal recurrent headaches, often one-sided and frequently accompanied by nausea and vomiting, were noted by Aretaeus in the first century A.D.

These are the commoner and more important allergic diseases. Some are of ancient lineage, and we may infer that the others are no younger even though first recognized and described as such much more recently. The symptoms of these six maladies are so different, one from the other, that it is small wonder that no one suggested a possible relationship between them. Why should a person with occasional headaches suspect that he is suffering from the same disease as one with hay fever, or another with eczema of the feet, or yet another who knows quite definitely that his stomach-ache is due to oysters?

Trousseau's Exudative Diathesis

Fifty years before the birth of the allergic concept a few physicians with clear perspective suspected some relationship even though they couldn't see any reason or justification. Notable among them was Trousseau, the great French clinician of the mid-nineteenth century, who regarded asthma as part of a 'diathetic neurosis,' other diseases within the diathesis being eczema, hives, rheumatism, gout, gravel, hæmorrhoids and periodic headaches. Of course he was wrong on gravel and hæmorrhoids and probably only partially right concerning gout. But why did this keen observer suspect a relationship between these so dissimilar diseases? There were two reasons. A person might have eczema at one time, sick headache at another. When two or more of Trousseau's diathetic symptoms were present in one individual they were likely to alternate with each other. The second reason was that although these diverse manifestations might not occur in a single person they might appear in different members of a single family. There appeared to be a familiar relationship between them which raised the question of an hereditary tendency.

The term *diathesis* is no longer used in modern medicine. It means a natural or congenital predisposition to some special disease or group of diseases. One spoke for example of the tuberculous diathesis or the rheumatoid diathesis. The implication was that a predisposition toward the development of a certain disease was recognized but that the reason was not completely understood. The term was coined to imply this fact. As soon as the condition became more clearly delineated the word was no longer needed.

This was the situation toward the end of the nineteenth century, when events of tremendous importance to allergy were occurring in medicine.

Chapter III

A VERY SHORT HISTORY OF MEDICINE

THE INTELLIGENT STUDY OF DISEASE WAS BEGUN BY HIPPOCRATES, who lived four centuries before Christ. Many Greeks and Romans whose names are traditional in medicine contributed to our knowledge. Among them was Galen, whose teachings, both correct and erroneous, controlled medical thought through the Dark Ages. For over eight hundred years none dared question his authority.

With the renaissance of art and literature came renaissance in medicine. Vesalius, the first great anatomist, studied the structure of the human body. In his voluminous writings he proved the error of the earlier Galenic anatomy. The year 1600 found a young English student, William Harvey, at the University of Padua, working under a successor of Vesalius. This young man proved for the first time that the blood circulates, flowing out through the arteries and capillaries and back through the veins to the heart.

This was important enough, but far more important was the fact that Harvey proved his theory by means of laboratory experiments. In this way he introduced a new method for the study of disease. Before his time physicians *observed* and attempted in a philosophic way to interpret what they saw but made no effort to reproduce the phenomena in a laboratory, so that they could be studied more accurately and in greater detail than would ever be possible when working with human beings alone.

By the middle of the seventeenth century doctors had accurate knowledge of human anatomy and an ever-increasing understanding of physiology, the vital activity of those anatomical structures which comprise the body. Now they became curious concerning the effects of disease on these structures. Vesalius and others had found abnormal conditions at autopsy but had given them little attention, being more interested in the normal. The study of pathology, those changes in anatomy resulting from disease, was inaugurated by a group of practising physicians who studied their patients during life, seeking all discoverable evidences of abnormality, and then followed them to the autopsy table, there to correlate their earlier observations with the abnormal changes found after death. Having discovered certain abnormalities, having studied certain symptoms during life and having later found that certain organic structural changes in the kidney, heart or elsewhere invariably accompanied the observed abnormalities and symptoms, they were able, then, to reverse the process.

Seeing another patient who complained of the same symptoms,

they could reason: "This patient has a headache, shortness of breath, swelling of the ankles and palpitation. His heart appears to be enlarged and his arteries are hardened. We have found albumin in the urine. Another patient whom we once saw with the same complaint and with the same abnormal findings was found at autopsy to have diseased kidneys, hardening of the arteries and a dilated heart. Therefore this man in all probability has the same disease."

Improvements in the treatment of disease necessarily lag behind advances in our understanding thereof. Although modern methods of study date from Vesalius and Harvey, modern treatment is more recent. In the last quarter of the eighteenth century a group of famous clinicians, led by John Hunter, the great physician of his day, at last placed treatment on a scientific basis.

What is Diagnosis?

Our brief survey of the history of medicine has brought us to the opening of the nineteenth century, when diagnosis by scientific procedure was advancing apace. Diagnosis is derived from two Greek words, *dia* and *gnosis*. *Gnosis* means knowledge. *Dia* may mean either apart or through. We may interpret diagnosis as 'knowledge apart' or, less literally, 'the art of distinguishing one disease from another.' Or, using the other significance of the first syllable, we may define diagnosis as 'knowledge through,' or thorough knowledge or, less literally, 'a clear understanding.' Although the former definition is found more often in the dictionaries, I prefer the latter. One might even combine the two. Certainly a diagnostician should be one who understands clearly and can differentiate one disease from another.

Even at the beginning of the nineteenth century there remained much that was not clearly understood. Certain symptoms had been found associated with disease in certain organs or tissues. Physicians produced these diseases in experimental animals, then tested the effects of drugs which might be used in treatment. The causes of some diseases could not be discovered at autopsy. A person with sick headache no longer has it after death. Autopsy showed no disease in the brain or elsewhere to account for the headaches. Hives or urticaria does not persist after death and its pathology remained in great measure unknown. The same may be said of hay fever, angioneurotic œdema and food idiosyncrasy and, to a limited extent, of asthma. This was curious, for it seemed reasonable from past experience that every disease should cause permanent structural alterations. Of course one might argue that these are not fatal diseases and that persons who have them finally die from other causes. Nevertheless, the absence of organic changes gave these ailments an air of mystery.

The Cell is the Unit of Life

The pathologist studied the results of disease. He could remove an organ, hold it in his hand, examine it and cut it up to see what it looked like on the inside. The next great advance which carried us much farther was the discovery of the microscope. It was first used for the study of tissues by Johannes Müller in 1830, not much over a hundred years ago. Müller found the tissues to be composed of many little individual structures which he called cells. He could see them but he could not study them very accurately because lenses were not very good at that time. They appeared as pale things and showed no definite inner structure, for the methods of staining cells to make the component parts visible had not yet been developed. In 1831 Schleiden proved that plants are made up of aggregations of cells, and seven years later Schwann, a pupil of Müller, established the same fact concerning animal tissues.

Now we had a new concept of the unit of life. Instead of arguing, as did the ancients, over whether man's soul and the seat of life were located in the heart, the brain or the liver, we became aware that the ultimate unit of life is the living cell and that the life of the individual depends upon the harmonious activity of the entire cellular aggregation.

The microscope provided opportunity for more minute study of pathologic processes. Study of the cellular pathology of disease was inaugurated about 1850 by several scientists, led especially by Rudolf Virchow, a German. We could now speak of gross pathology when an organ is examined as a whole and of microscopic pathology when the cells themselves are studied. Possibly some of these curious maladies which showed no gross organic changes recognizable to the naked eye might show microscopic cellular changes. Some of them did.

Bacteria are Cells

In the twenty-odd centuries since the days of Hippocrates there is no single century, nor any half-dozen, which has witnessed as great and rapid progress in the study and treatment of disease as have the last hundred years. This period was inaugurated ninety years ago with the introduction of the microscope in medicine. The instrument made possible the science of bacteriology. The epochal studies of Louis Pasteur led to the realization that very small living cells, called bacteria, may cause disease. This great scientist also proved that man could be immunized against bacteria. From this point on, pathology and bacteriology proceeded hand in hand, the bacteriologist discovering those germs which cause illness, the pathologist determining the manner of their propagation and their destructive activity within the body.

Yes, great things were happening in medicine toward the end

of the nineteenth century. Research laboratories were regular beehives of activity. Men were looking down through long tubes, studying tremendously enlarged cells, bacterial, human and animal. New bacteria were found to be the causes of one ailment after another. The feverish activity of the scientists of the day was directed toward proving a bacterial agent for every disability. The allergic diseases were not exempt from this onslaught.

First Steps in Immunity

The field of immunity was developing along parallel lines with that of bacteriology. Edward Jenner, an Englishman, had successfully vaccinated against smallpox in 1796. It is difficult for us to-day to realize what that meant. Before the days of Jenner at least sixteen of every hundred persons in London were covered with pockmarks. The resulting disfigurement was sometimes quite awful. There was another malady which affected cattle and was called cowpox. Milkmaids often contracted cowpox, but it was a mild disease which affected only the hands. Jenner had noticed that milkmaids who had had cowpox never developed smallpox. He had also observed that cowpox never developed into smallpox. So he inoculated humans with cowpox in order to produce a little local disease like the present-day vaccination reaction. He discovered that, as with the milkmaids, this protected against the more devastating illness. This is what we do to-day. We do not immunize against smallpox by inoculating with smallpox virus. We inoculate with the virus of cowpox. The two germs are so nearly alike that immunity against one protects against the other.

The word vaccine is derived from the Latin *vacca*, meaning cow. The first successful vaccination with scabs from sick cows produced this new word. Since then we have used vaccination as synonymous with immunization even though the cow may play no part in protecting against the disease which we are trying to prevent.

Jenner was not the first. The Chinese, three hundred years before Christ, used scabs from mild cases of smallpox to protect others against this plague. I presume that the earliest savages discovered by accident that they could safeguard themselves against the effects of the poisons used on their spearheads. Probably they drank infusions of the plants from which the poisons were made, gradually increasing the strength of the concoction until they could at last tolerate what would otherwise be fatal doses.

Knowledge of the possibility of increasing resistance or immunity to harmful agents must have existed in ancient times if we are to believe the story of Mithridates, King of Pontus. Distrusting his many enemies, he caused himself to be immunized against all known poisons. But, like poor Achilles, his precautions were of little avail since Mithridates eventually died by his own sword.

Jenner knew little more than the King of Pontus or the savages

as to why vaccination established protection. He was a keen observer and a fortunate experimenter. Nearly a century was to elapse before anyone understood the mechanism of immunity.

Chapter IV

A CHEMIST EXPLAINS IMMUNITY

INTO OUR STORY NOW ENTERS THE SCIENCE OF CHEMISTRY.

One might well wonder why doctors were not satisfied with discovering nearly all that is to be known of the structure of the human body, learning much concerning those changes in its organs and tissues which result from disease, proving that the ultimate unit of life is the living cell and finding that alterations in the vital processes of these cells, due to ageing, bacterial injury, poisoning and other causes, are the basis of disease. Why look further when one cannot see things too small to be resolved by the modern high-power microscope? But clever scientists realized that with indirect methods the search could be continued.

Protoplasm and its Activity

Biochemists, who study the chemistry of the processes of life, soon discovered that the basic unit of every living cell is an extremely large and complicated chemical molecule known as protein. Aggregations of protein molecules, bound together with molecules of non-living structural compounds—fats, sugars, starches, minerals, etc.—constitute the cellular protoplasm which is that part of the cell seen in the microscope. They also found that living protoplasm is in a state of constant activity, absorbing chemicals into the cell either for food or for repair of damaged structures and excreting waste products, those chemicals which have been used and are no longer needed. In a chemical sense constant change is characteristic of the processes of life. A cell in which all activity stops is no longer alive.

Here, then, is a method, beyond that of the microscope, with which one may study how living cells work, how they alter their activity when injured or diseased and how they protect themselves against further injury. Here, indeed, is an opportunity to learn what happens when cells become immunized, when they learn to protect themselves against harmful influences. Fortunately much of this study can be done through examination of the body fluids, especially the blood, since the blood is, in essence, a delivery system carrying needed food and other chemical compounds to remote cells and in turn carrying their decomposition products away to the lungs, kidneys or bowels for eventual disposal outside the body.

One may determine what substances that were present in the blood of the arteries are absent from the venous blood which has passed through the tissues. Whatever is missing was used by the cells or was excreted. Similarly, substances that are present in the veins and not in the arteries must have come from the tissue cells. It doesn't work out quite this easily, but the principle is correct.

Bacterial Activity

Jenner had successfully vaccinated against cowpox, using scabs from infected animals. He knew nothing of bacteria or the still smaller forms of life known as viruses. He made no attempt to separate or purify any possible causative agent in the laboratory. He could not have done so because the laboratory facilities were not yet available. Pasteur did do this. He grew the abnormal little cells which he had seen in the blood of sheep dead from anthrax. He found these cells only in sheep infected with anthrax, not in normal ones. Quite naturally he postulated that they must have something to do with the disease. He put drops of the sheep's blood into tubes of broth which he had sterilized by boiling and found that the chains of abnormal cells increased in number until they very nearly filled the tube. He would then transfer a drop from this tube into a fresh tube of sterile broth and the same thing would happen. This could be repeated with tube after tube. Evidently the little cells must be growing and reproducing. In other words, they were alive.

Protection against Bacteria

Pasteur found that if he injected his anthrax bacillus into normal sheep they soon died of anthrax. Following the precedent of Jenner, he then tried to immunize the animals so they would be no longer susceptible. If he could injure the germs to such an extent that like a partly vanquished army they could do little damage, he might be able to train the body cells to protect themselves against this enemy. This might be done by heating the protoplasm of the germ enough to injure it but not quite enough to kill it. The same could also be accomplished by chemical methods. Pasteur injected this attenuated or weakened vaccine into normal sheep. After several such treatments he injected virulent unattenuated anthrax bacilli. For his final experiment he used fifty sheep. Half had been protected with his vaccine while the other half had had none. All received injections of virulent bacilli on May 31, 1881. Two days later Pasteur's triumph against the many doubting Thomases was complete. The carcasses of twenty-two unvaccinated sheep lay on the ground while two others were near death. The twenty-fifth died in the night. The twenty-five vaccinated sheep remained in perfect health.

In this way it was shown that Jenner's success in vaccination

must have been due to the introduction of the same germ or a very closely related one whose invasive power was diminished. In the interval between the first injection of the harmless vaccine and the final injection of the virulent germ—an interval which later investigation showed must be several days, usually ten or more—the body cells must have developed some mechanism by which they could protect themselves against this harmful environmental influence. They had immunized themselves.

Pasteur's success with anthrax was repeated with rabies, and other investigators similarly immunized against typhoid fever, Asiatic cholera and, to a lesser extent, against whooping cough and tuberculosis. Vaccines have been used with varying success in other diseases. It should be borne in mind throughout this book that the term vaccine applies only to material containing the germ which causes the disease, altered in one way or another so that it is no longer dangerous. A 'serum' does not contain this substance.

The next question, an obvious one, was how do the cells change their activity to protect themselves against the germs? An answer was provided by Ehrlich.

The Founder of a New Method of Treatment

Paul Ehrlich was a German physician and chemist. Devoting his life to research, he contributed more to medical chemistry than any man who has lived before or since.

The alchemists of the middle ages, with the little knowledge of chemistry that was available in their day, had sought to transmute the baser metals into gold. Paracelsus, a bombastic Swiss doctor-alchemist who lived from 1493 to 1541 and who, as a consequence of his arrogance and his outspoken views, found himself in difficulties wherever he went, was the first outstanding chemist to lose interest in the search for gold in favour of search for chemicals which might be used in the treatment of disease. His great discovery was the therapeutic value of mercury. Prior to the time of Paracelsus and for long thereafter physicians sought for curative drugs mainly from the vegetable kingdom. During the period after the renaissance of medicine many were the discoveries of utmost value derived from plants. Quinine, cocaine and digitalis, drugs which are irreplaceable in the medicine of to-day, are outstanding examples. Within the last twenty years ephedrine, a chemical which is extracted from a Chinese weed and of utmost importance to persons with allergy, has been added to our list of useful remedies. We may see, then, that this branch of pharmacology, the study of drugs, is not yet a closed chapter. But this was not the field of Ehrlich's interest.

From the time of his earliest medical research Ehrlich's approach was that of the chemist. He first became interested in the action of aniline dyes, their use in the laboratory and in the treatment of

disease. He discovered that one dye was valuable in the treatment of trypanosomiasis, an infectious disease. He continued to investigate the possibility of chemical treatment of such diseases. Whenever he found that a certain chemical gave promise of curing some infection artificially induced in a laboratory animal, he would change the chemical by adding on an extra atom of sodium or chlorine or some other element, or by combining two separate chemicals to form a single new hitherto unknown molecule. His discovery of salvarsan, one of the drugs now used in the treatment of syphilis, was alone enough to make him famous through the ages. But he did many more things before his death in 1915.

New Drugs are Invented

Ehrlich established the new science of chemotherapy, the treatment of disease with synthetic drugs which are created in the laboratory for this specific purpose. He perfected what Paracelsus had started. The most recent examples are sulphanilamide and sulphapyridine, those remarkable chemicals which have been so surprisingly effective in the treatment of certain streptococcus and pneumococcus infections as well as other diseases. The manner in which sulphapyridine was developed appropriately illustrates the methods used in chemotherapy. Sulphanilamide is a by-product of the aniline-dye industry. It was found to be very effective in the treatment of some types of streptococcus infection. Theoretically it should have done as well in pneumococcus pneumonia. But it didn't. New compounds were therefore prepared, with sulphanilamide as the point of departure—as the foundation for these previously non-existent chemicals. In all, sixty-four compounds related to sulphanilamide were tried. It was found that a combination of sulphanilamide with pyridine is as effective against the pneumococcus as sulphanilamide is against streptococcus.

Ehrlich's Theory of Immunity

Being interested as Ehrlich was in the prevention and cure of infection by chemical means, it was but natural that a theory of immunity proposed by him should be expressed in chemical terms.

The chemical basis of life is the large complex protein molecule. It consists of many simpler elements more or less closely attached to each other, the most important of which are termed amino acids. That unknown factor which we call *life* endows the protein molecule with ability to attract to it those chemicals which, for continued existence, it must build into its structure. Life is a process of wear and tear, repair and rebuilding. The living protein molecule is constantly breaking down here and there in its structure. Parts are replaced, new amino acids and other chemicals being incorporated into the molecule. This is the manner in which, speaking chemically, the living cell feeds itself.

What would happen if the molecules of a cell, reaching out as it were to get food, were to grasp some chemical element injurious to themselves? The molecules would be damaged.

The physiology of the human body is arranged to protect its

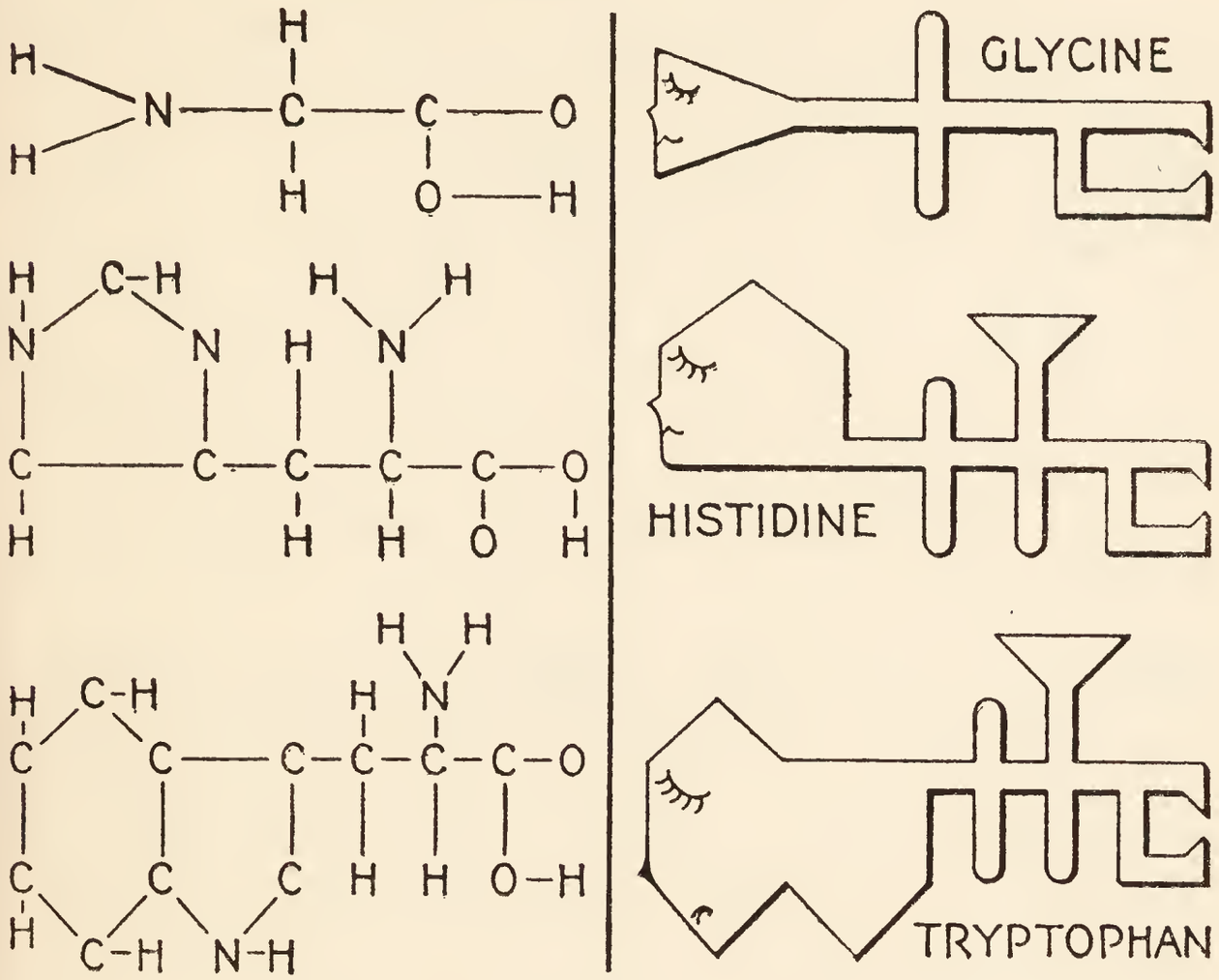

FIG. 1

AMINO ACIDS

Simplified chemical formulas (left) for three amino acids. C stands for carbon, H for hydrogen, O for oxygen, N for nitrogen. The lines connecting these elements indicate actual chemical connections, just as the formula for water (H_2O) may be written H-O-H, indicating two atoms of hydrogen attached to one of oxygen. The complex nature of amino acids as compared with a simple chemical such as H_2O is obvious.

Amino acids are chemicals without visible form, except when crystallized. We might indicate them pictographically (on the right) as having somewhat the same shape as their chemical formulas (left). Each amino acid differs from every other amino acid. Each has an acid-reacting portion and an alkaline-reacting portion. Two amino acids may become combined to form a single larger chemical by union of these two opposites (acid and alkaline).

The acid part of the molecule is at the right end of the chemical formula (COOH) and is represented at the right end of the pictograph by a pincer. The alkaline or basic part (NH_2), at the left end of glycine and the top of histidine and tryptophan, is pictured (right) as a wedge. The union of two amino acids is accomplished by a pincer grasping a wedge.

Living protein consists of a very large number of amino acids attached to each other. Amino acids, alone, are not alive. This is indicated in the pictograph.

cells against such contingencies. The skin and mucous membranes serve as barriers against the penetration of harmful substances. The digestive juices break many potentially harmful substances down into simpler harmless compounds which are then absorbed

through the intestines into the blood. The blood normally contains nothing which is injurious to living cells.

Foreign Proteins

In the presence of infection this is no longer true. Bacteria, which also contain complex living proteins foreign to normal

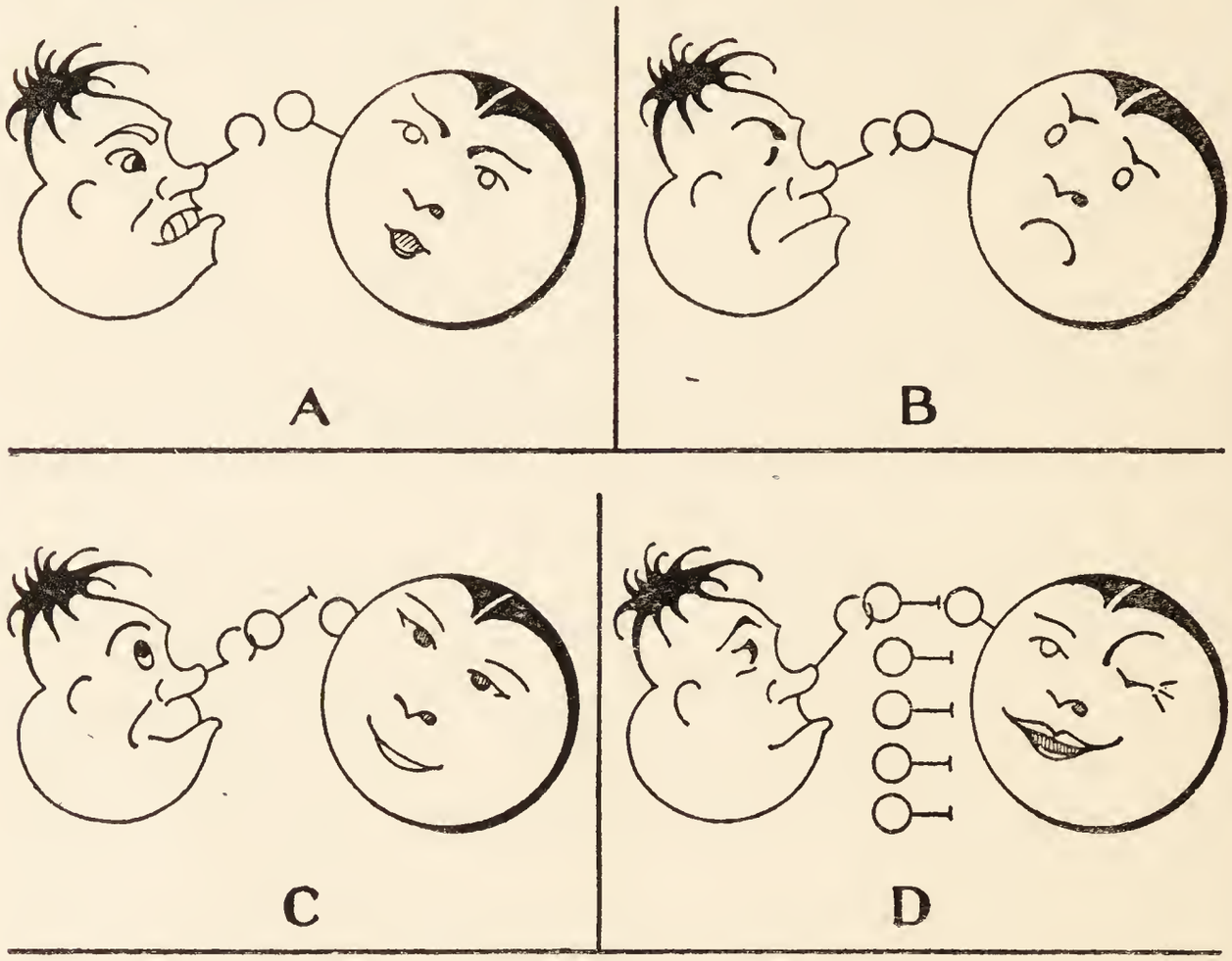

FIG. 2

RECEPTORS (ANTIBODIES)

Foreign protein combines with the protein of living human cells by attaching itsel to receptors which are presumably part of the human protein molecule (A). This injures the human cell (B). To protect itself the cell releases or sheds the receptor which presumably remains attached to the foreign protein (C). The human cell promptly starts to produce a new receptor to take the place of that which has been lost.

Gardeners know that if you want to produce dense foliage you must clip the ends of branches. When this is done dormant buds become active and many smaller branches grow out to take the place of the ones which were clipped.

This same idea may be applied to protective antibodies. If one receptor is injured, the cell will produce many more to take its place, so many that some are shed from the cell and float freely in the body fluids. These receptors are called antibodies (D). If the same foreign protein now enters the blood, it meets free-circulating or floating antibodies which combine with it, neutralizing its attraction toward the living cell, thereby protecting the latter. This is immunity.

human cells, may come into intimate contact with the latter. If chemical combination occurs the human cell is damaged.

In order to rid itself of this harmful chemical the molecule destroys or releases the connecting link. But let us suppose that the attraction between the bacterial molecule and the human molecule is so strong that the attachment, having been formed,

cannot be broken at that point. An obvious solution to the problem would be to sever the connection at the next link in the human molecule. This damages the cell somewhat but not as badly as continued connection with the bacterial protein would do. Of course, the cell will be short one link, but it can repair itself and does do so.

Now a foreign protein such as bacterial protein, harmful to the human cell, is not equally attracted to all of the possible points of attachment in the human molecule. There are many terminal links of this complicated molecular chain, each comprising a possible point of contact for those chemicals which are to be built normally into the molecule. Each one may differ from the others to such an extent that the bacterial protein will attach itself only to one particular link. This link will then be shed. To protect itself the molecule not only rebuilds the lost link but makes a large number of them, all alike, and continues to loosen or shed them. If, later, another identical bacterial molecule appears in the neighbourhood, it will be attracted to some of these free, unattached links. When it combines with an unattached link its chemical appetite in that direction is satisfied to such an extent that it will no longer become attached to the living cell. The cell has established protection by surrounding itself with a large number of loose links.

This is the basis of the Ehrlich side-chain theory of immunity, very much simplified. The defensive links of the chemical chain are called antibodies. The antibodies are manufactured by the cell for use against harmful substances, particularly harmful foreign protein. The foreign protein itself is termed antigen, which literally means something which generates or causes the production of antibodies.

How It Works

Let us simplify the picture still more. I shall be the human cell. A vicious dog will take the place of the harmful germ. I am walking peacefully in my walled garden. In one hand I have a stick with which to knock apples out of the tree so that I may eat them. In the other I have a small spade for digging my potatoes. If I had more hands I might have other instruments, all different and designed for procuring different types of food.

Enter the savage dog. He comes at me. I defend myself with the stick. He bites the stick. The best thing for me to do is to release the stick. He can have it. I then find to my surprise that he is not so savage after all. He is quite content to play with the stick and as long as he has it he is not interested in me. Surely I have found a way to protect myself. I shall make many sticks just like the first and scatter them about the yard. When the dog shows up again he doesn't go for me. He goes for the stick, and all is well. I have protected or immunized myself against dog

trouble. I am safe, but since I do not know when the dog may return I continue to make sticks, scattering them about.

Another animal, say a bear, might prefer spades. If I ever have an experience with a bear I shall certainly learn to make spades.

The Protective Antibody

No one has ever seen an antibody. We know antibodies not by what they are but by what they do. If a person becomes infected

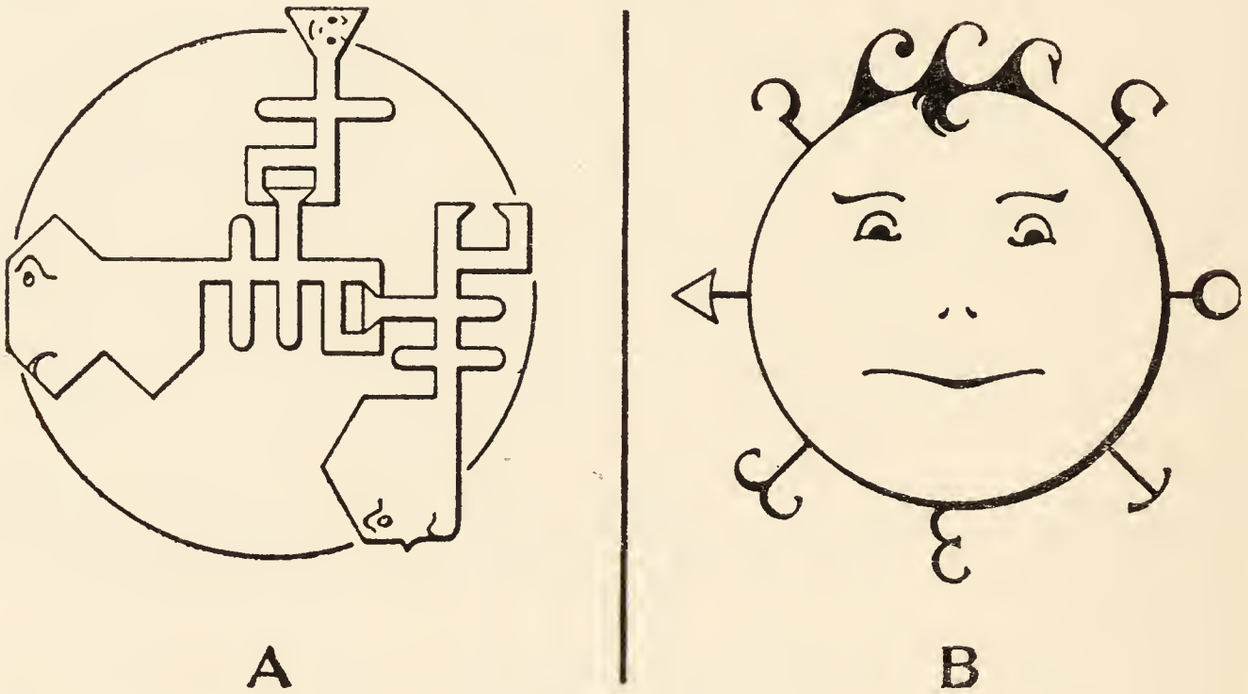

FIG. 3

THE CELL AND ITS ANTIBODIES

(A) *The protein* of a living cell consists of very many amino acids joined together chemically. Only three are shown in the illustration. This is far too few to give 'life' to the cell. Note that there are still unattached acid and basic radicals (wedges and pincers) for additional combinations.

(B) *Antibodies (receptors).* These hypothetical points of connection between living cells and substances in their environment (especially proteins) are much more complex than the amino acids. Each antibody probably consists of many amino acids, possibly enough for it to be a rather simple protein.

As far as immunity (or allergy) is concerned, every different foreign protein is matched by an antibody which differs from all other antibodies (see illustration). This explains why immunity against typhoid does not protect against pneumonia.

For simplicity only one antibody symbol will be used hereafter, even though different antigens may be discussed.

with the germ of typhoid fever nothing happens as far as he is concerned for about ten days. During this interval blood cultures will show that the germs are growing actively, reproducing in the blood, but the victim is not ill. He is unconscious of anything wrong. At the end of this ten-day incubation period the initial symptoms of typhoid fever make their appearance. According to the theory it takes about ten days for a sufficient number of typhoid-bacillus antibodies to be manufactured by the body cells to start to neutralize the activity of the typhoid protein. The original combination of typhoid protein with human cell protein causes no

symptoms even though it appears to be damaging the cells. This we will find is also true during the process of allergic sensitization.

At any rate, shortly after the symptoms of typhoid fever commence a new substance may be found in the patient's blood. From

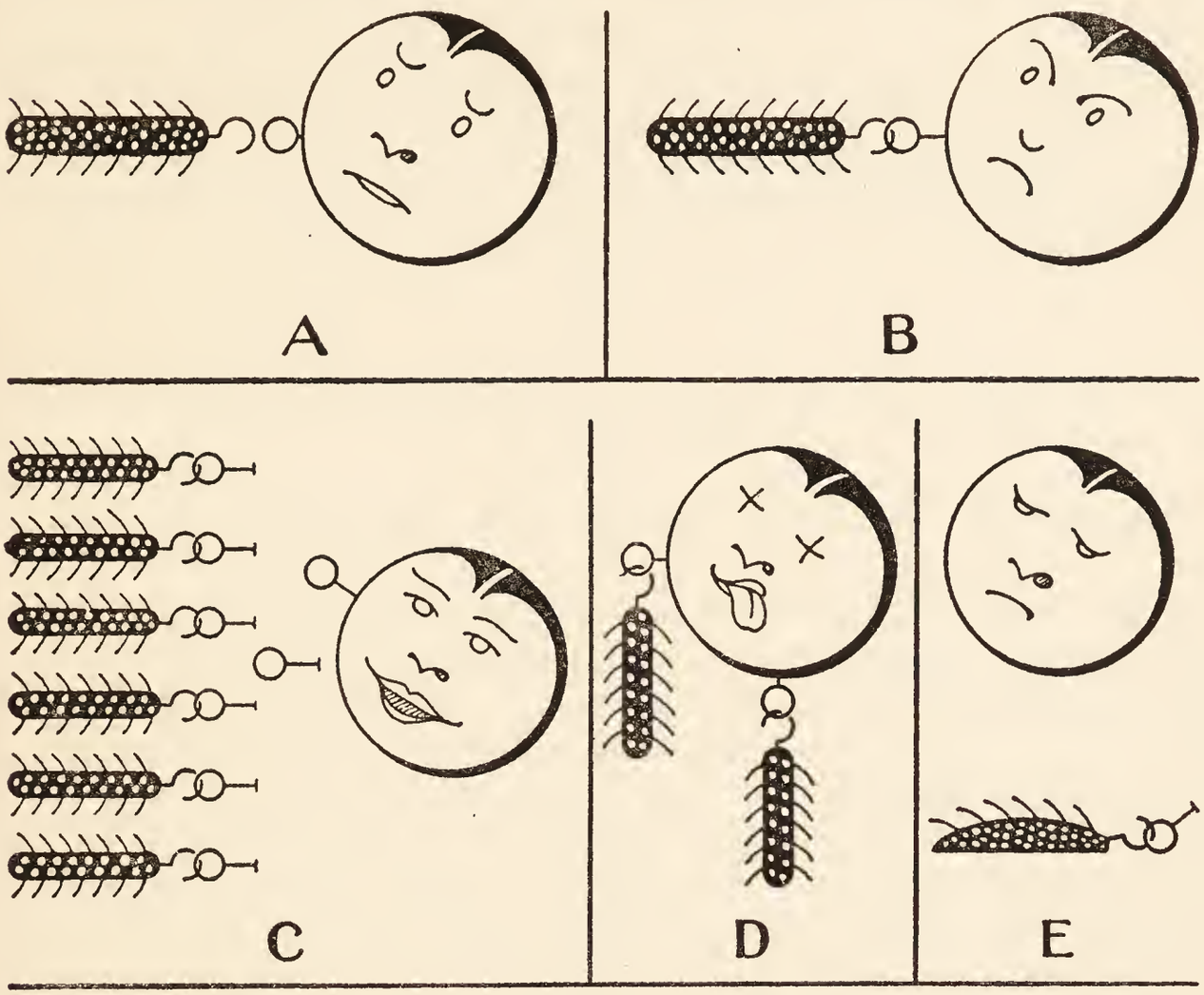

FIG. 4

THE MECHANISM OF IMMUNITY

The typhoid bacillus is carried in the blood to the human cell (A). Typhoid protein becomes attached to human protein, injuring the latter (B). The cell produces a surplus of antibodies which it sheds. When many bacilli enter at some later time, they are neutralized by floating antibodies (C). Some may pass this protective barrier. If too many do so, there is cell injury and the patient becomes ill with typhoid (D).

If, on the other hand, the majority of bacilli are neutralized by floating antibodies, the body cell is protected. Some few may get by and injure the cell slightly, but the floating antibodies, neutralizing the affinity between typhoid protein and human protein, destroy the activity of the former. The struggle works both ways. Typhoid bacillus attached to human cells injures the latter. Also the typhoid bacillus is injured. Floating antibodies injure it in the same way. With enough floating antibodies all of the bacilli are destroyed and human cells are protected (E). Vaccination consists of injection of small amounts of typhoid protein (A) which stimulate the body (B) to produce large quantities of floating antibodies (C) so that if later the body becomes infected with living bacilli the latter are destroyed (E).

this time on, and indeed after recovery from the illness, if the serum from the blood be mixed with typhoid bacilli in a test tube, the bacilli will clump together and die. Since this new substance makes the bacilli stick together as though glued it has been termed agglutinin. It indicates that the immunity mechanism is becoming active. The agglutinin, or precipitin as it is also called, must be

present in the serum, although no one has seen it. We know from what happens in the test tube that something new is there and that this new substance has something to do with immunity. Agglutinin, or precipitin, is either the same thing as antibody or else it is a very closely related substance which accompanies antibodies.

There are many weak points in the side-chain theory, but it has the advantage of relative simplicity and is still the accepted explanation of immunity even though scientists realize there is much that it does not explain and that another theory will eventually be forthcoming to take its place. Our interest in it lies in the fact that, as we shall see, it also explains much of the mystery of allergy.

Chapter V

ANTITOXINS AND SOME STRANGE REACTIONS

IF EVERY PERSON WERE TO RESPOND AS DID CAROLINE TO THE FLAX seed, allergy would be a very dreadful disease. Hers was an extreme example of a most unusual type of reaction. I shall tell of other extreme cases, not for their theatrical effect but because it was this explosive response that finally provided the solution of the riddle of idiosyncrasy, thus leading to an understanding of allergy. All illustrative cases in this volume are authentic, culled from our experiences and those of other physicians, modified only in minor points so that in the telling of the tale the victim need have no fear of embarrassing recognition.

Serum Disease

The most devastating allergic reaction is that which may follow the injection of curative serum. Fortunately it is rare. When it does occur one is again reminded of the strangeness of a disease which may be caused by a curative medicine. A friend, depended upon in time of need, turns out to be a vicious enemy.

Mr. Black had had a sore throat for a day or two. When he discovered that he had a fever and was really ill he called his doctor. The doctor promptly found the tell-tale greyish membrane of diphtheria. He swabbed the throat with a small wisp of sterile cotton, obtaining material for laboratory examination and, since there was no doubt of the diagnosis, injected diphtheria antitoxin. Within three minutes Mr. Black was unconscious, apparently about to die. The doctor, recognizing the condition as allergic shock, promptly gave his patient several injections of adrenalin, saving his life.

Another patient similarly affected called his physician, who realized the possibility and dangers of sensitization and therefore

gave an extremely small dose of antitoxin in order to make sure that no unpleasant symptoms would develop. He injected one one-hundredth of a cubic centimetre into the skin. The amount corresponds to about one-seventh of a drop. Surely this was so little that it could not possibly cause trouble. Five minutes later his patient was dead from allergic shock. Even the seventh of a drop had been too poisonous.

A child was ill with diphtheria. The doctor considered it wise to give prophylactic or preventive injections of antitoxin to all members of the family. The child's father, who was still quite well, dropped dead shortly after receiving his injection.

One of the most pathetic of these unusual experiences occurred in a doctor's family. Since the cook had diphtheria the doctor wished to give prophylactic injections to his twin daughters. One had been subject to hives. Realizing that she might be allergic, he hesitated to give serum. To the other twin with no allergic history he gave 1,000 units, the regular dose of diphtheria antitoxin. Within five minutes she was dead.

Severe or fatal reactions from curative serums are rare, although probably not as rare as the reports in the medical literature would lead one to believe. Dr. Robert Lamson found only forty-four cases of fatal allergic shock described between 1893 and 1929. Between 1924 and 1936 Dr. Pipes and I found sixty-nine reports of severe shock or death. Although the majority were deaths from serum, other allergens were responsible in some instances. When one realizes the tremendous number of preventive and curative hypodermic injections given every day the number of reactions is very small. The late Dr. William H. Parks, analysing a series of 350,000 serum injections, concluded that there might be a fatal reaction once in every 50,000 and a severe but non-fatal reaction once in every 20,000 treatments. The method of giving the serum plays some part. When it is injected directly into the vein, reactions occur about once in every seven hundred treatments. These are not necessarily fatal.

Serum disease, as this is called, is a man-made malady. If we had no curative serums and if there were no such thing as a hypodermic syringe with which to introduce the material under the skin, there would be no serum disease. Instead multitudes would still be dying from diphtheria and lockjaw and several other infections. Thus we find ourselves in somewhat of a dilemma, faced with the necessity for choosing the less of two potential evils. Fortunately, with an adequate understanding of allergy and with improvements in methods of purifying serums, the risk to-day has been reduced almost to the vanishing point.

Before 1893 there was no such medicine as diphtheria antitoxin. Curative horse serum was not being injected into people. Consequently there was no such malady as serum disease. Serum

sickness interests us not only because it is an expression of the allergic state but also because it was the first disease recognized as being allergic.

Sewall's Snakes

The drama of the discovery of antitoxin starts in the late 1880's. We find the first actor, Dr. Henry Sewall, in a dark little laboratory in Ann Arbor. Dr. Sewall was professor of physiology at the University of Michigan. He was one of the first men in the world to be made a professor of physiology. This was a new branch in the teaching of medicine. While Sewall's duty was to acquaint his students with the normal workings of the human body he was equally interested in the abnormal, since this provided a clearer insight into the normal. In his investigations he made many curious experiments.

In the 1880's he was studying the action of snake venom. He would tease his snakes until they were thoroughly annoyed and then would slip a small porcelain dish with a very long handle down into the cage. The snakes would bite at the dish. He would then withdraw the dish. In it was the poisonous secretion. The venom manufactured in the snakes' poison glands was excreted through the fangs at the moment when the snake had struck. The fangs are hollow teeth somewhat like two hypodermic needles.

Dr. Sewall next injected the venom into pigeons. Of course it killed the pigeons. But he wished to learn whether he could immunize them. He started giving very small quantities, highly diluted. He gave the injections frequently and gradually increased the dose. In this way he immunized the birds so successfully that they no longer died when bitten by the snake. This was a most important discovery. It meant that, using Pasteur's method for immunization against bacteria, animals could be made resistant to a non-bacterial poison manufactured by an animal.

Calmette's Birds

Soon thereafter Dr. Albert Calmette of the Pasteur Institute in Paris proved that the birds had gained their immunity by producing a substance which could be found in their blood and which was antagonistic to venom. He called it antivenin. It was a second kind of antibody, made by the body cells in the same manner as bacterial antibody and explained in the same way by the side-chain theory. There was only this difference, that the substance against which protection was created was a poisonous *secretion*, or product of cellular activity rather than the foreign protein of the cell itself. Immunization against typhoid fever implies a defensive weapon against typhoid bacillus protein. The pigeons were not immunized against rattlesnake protein. They were protected against a poison manufactured by rattlesnake cells, a chemically different substance.

Antivenin is widely used to-day by those who have suffered

snake bites. It is made by injecting venom into horses. Horse cells manufacture the protective antibodies so plentifully that they abound in the blood. Blood is withdrawn from the horses' veins and the serum, the liquid part, is separated from the clot. It is further purified, distributed into sealed glass tubes and is ready for injection into the snake-bite victim. The horses were *actively* immunized, and their blood will continue indefinitely to contain

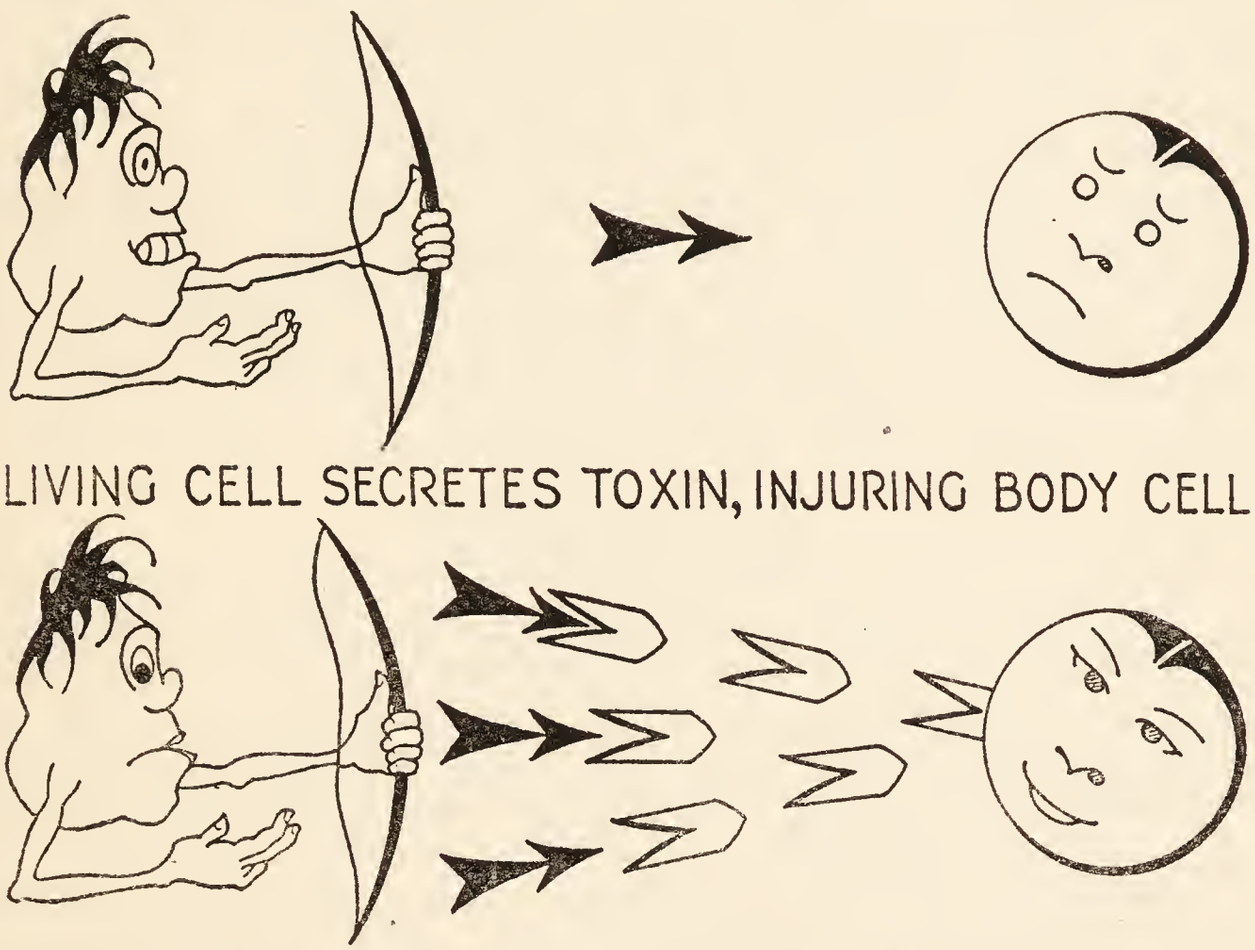

FIG. 5

TOXINS AND ANTITOXINS

A toxin is a protein or a substance very closely related to protein, formed and secreted by a living cell. We might speak of toxin action as injury of the human body cell by remote control. In other words, the snake cell need not necessarily come in contact with human body cell protein. It can manufacture a 'poisonous' protein which eventually comes in contact with the body cell. From here on the process of human cell injury and protection by the manufacture of floating antibodies is the same as with typhoid protein, illustrated in the preceding figure. Non-living antigens secreted by living cells which affect the human cell in this manner are called toxins. Toxins differ from ordinary proteins in that they are naturally poisonous. The first snake bite is as harmful as later ones.

antivenin. The man who receives a protective injection of serum is *passively* immunized. His cells have not learned to make the antibodies. He is protected only for so long as the horse antibodies persist in his blood. This averages about four weeks. Beyond this he is again susceptible.

Roux's Germs

Pierre Roux, who had been Pasteur's first assistant and later became director of the Pasteur Institute, now enters the sequence

of our story. One of the world's leading bacteriologists, he had been investigating a poison or toxin which is manufactured by the diphtheria bacillus. It is this toxin which, absorbed into the body, causes the severe symptoms of diphtheria. Roux, repeating Sewall's work but using toxin instead of venom, found that the former exerts its effects in just the same way. This was very important. Sewall had worked with a poison manufactured by animals, Roux with one made by bacteria. Both were toxins, both acted in the same way and both caused the production of antibodies. It remained for Paul Ehrlich to show later that vegetables, as well as animals and bacteria, could produce toxin. Injecting the poisons of castor bean and jaquerity bean into animals, Ehrlich found that protective antibodies will be formed. Toxin means poison, but in medicine we now define a toxin as a type of poison against which an animal may become immunized by the production of antibodies. There are other poisons, such as carbolic acid and bichloride of mercury, against which protective antibodies are not developed.

Von Behring's Horses

Next came Emil von Behring, a German. Von Behring duplicated Calmette's work but this time used diphtheria toxin instead of snake venom. Diphtheria antitoxin was produced. Here is the sequence : Sewall immunized pigeons against venom ; Calmette showed how it was done with antivenin ; Roux found that toxin works like venom ; and Von Behring applied these facts in the preparation of antitoxin.

Few of us to-day can realize what a wonderful discovery this was. Diphtheria was as horrible a disease in the nineteenth century as smallpox had been in the eighteenth. There was no cure. It was heartrending for doctors and parents to sit watching little children suffocate from the blockage in the air passages and be unable to do something about it. Antitoxin brought hope where there had been none.

It was in 1894, at the meeting of the International Congress on Hygiene and Demography in Budapest, that Von Behring announced his discovery. The medical savants of the world were gathered there. All knew the horrors of diphtheria. When the young German announced that he had immunized horses against diphtheria toxin, had injected the serum into children ill with the disease, had cured them as if by magic, what did these scientists do ? They did nothing. It sounded too good to be true. This young fellow was probably mistaken. But when a few minutes later Pierre Roux announced that he had checked Von Behring's work and that his conclusions were justified they knew it must be true. Then something happened that has probably never occurred before or since in any scientific meeting. Those staid and proper scientists rose and cheered, threw their hats in the air, slapped each other on the back

and behaved for all the world like a crowd of college youngsters whose home team had won a big football match. They knew what it meant. They realized that they had just heard the first announcement of one of the greatest discoveries of medicine for all time.

Dr. von Behring gave each of them a small vial of his life-saving serum. Thus it happened that my father was the first person to bring diphtheria antitoxin into the United States.

Soon the drug manufacturers were buying horses, growing diphtheria germs and extracting the toxin, injecting it into the horses and later collecting and purifying the serum. Antitoxin was soon available throughout the civilized world and the first and greatest step toward conquering this dread disease had been made.

All would have been perfect had it not been for the occasional unexplained catastrophes which followed antitoxin injections, such as those described at the beginning of this chapter.

Chapter VI

THE SEARCH FOR A HAY FEVER ANTITOXIN

SO MUCH FOR INFECTIONS AND TOXINS AND FOR METHODS OF PROtecting against these enemies of man. So much for explanations of how artificially induced immunity works, and so much for those rare, unexplained episodes in which this protection fails and the curative medicine becomes, instead, a deadly poison. These considerations seem a far cry from the garden varieties of hay fever, sick headache and hives. Nevertheless, they were a necessary prelude to an intelligent understanding of allergy.

Pasteur had started the fashion of searching for bacteria as causes of nearly all diseases. Hay fever did not escape. Von Helmholtz, the great physicist who was himself a hay-fever victim, believed he had discovered the germ. Several others, especially in Germany, held to the infectious theory. Even in 1902 this explanation was still the favourite in the leading German medical encyclopædia.

The discovery of the importance of toxins introduced yet another vogue—search for toxins causing those illnesses in which bacterial causes could not be found. Here, again, hay fever received its full share of interested study.

Pollens are Suspected

Bostock had, in 1819, described what he considered a new disease (see page 18). Twelve years later Elliotson suggested that pollen might be the cause. He did not offer any confirmatory

evidence. Shortly after the middle of the century another English investigator, Charles Blackley, entered the picture.

The majority of those who have made outstanding contributions to allergy have themselves been allergic. Blackley was no exception. As did others whose intimate personal acquaintance with the vagaries of the malady promoted clearer understanding, Blackley first suspected pollens when some flowers, shaken in his room, released a cloud of pollen dust. A few minutes later he was sneezing violently.

He must have been an unusual fellow. Pollens having come under suspicion, he devised all manner of clever experiments to prove their importance. Although his patients co-operated, he made most of his experiments upon himself. He continued these for over twenty years, and although he may have discussed them with his confreres, he wrote nothing. Apparently he was quite content to convince himself and had little interest in convincing the world.

It would have been unique for him to have been the only man interested in the possibility of a pollen factor. There was another investigator in the field, and a very good one. He was Professor Morrill Wyman, of Harvard, who for years had had hay fever in August and September. Each year, he, his son and his brother had found some relief at Bethlehem in the White Mountains. I don't know just how Wyman came to suspect ragweed pollen. Possibly he had noticed that while ragweed was abundant at home it was scarce at Bethlehem. At any rate, on a hot August day about 1870 he filled a small box with ragweed plants before leaving his home in Boston. After he and his party had been in Bethlehem long enough to be relieved each sniffed at the contents of the box. Promptly there was a return of symptoms. Other volunteers had the same experience.

This seemed pretty conclusive evidence against ragweed. There was one hitch in the experiment when in midwinter, with no pollen in the air, they again sniffed at a box of ragweed. They should have again had symptoms, but none appeared. The plants might have been picked after they had ceased pollinating.

Wyman was so convinced of the importance of ragweed in causing autumnal hay fever that, feeling that other physicians should know of this, he wrote a short book describing his investigations. It was published in 1872.

Then Charles Blackley emerged from his cloistered existence. Here was an upstart from the New World who with a few very elementary experiments was claiming that pollens cause hay fever. After the work of a few weeks or months at the most he was jumping at conclusions that Blackley had taken twenty years to prove. Certainly it was high time for Dr. Blackley to assert himself. And assert himself he did with a book published in the following year,

1873. He had little to say of Wyman's work except in an unfavourable way. Certainly pollens caused hay fever, but Blackley, not Wyman, had established the fact. Furthermore, Blackley knew that it was the pollen of grass, not of ragweed. Indeed, he didn't know what ragweed was. He had never seen it. Regardless of the dispute, and aside from the fact that Blackley was subject to honest criticism for his indifference in not notifying his colleagues of his very interesting observations, the medical world now very properly gives him credit for having proved the pollen causation of hay fever.

The Evidence Against Pollen

When he at last published his work it was at once obvious that he had covered all possible contingencies and criticisms. Not only had he sniffed grasses in and out of season as Wyman had done, but he had collected pollen, sniffed it to produce hay fever, and rubbed it in his eye to produce conjunctivitis, which often accompanies the disease. He also had rubbed a little into a scratch on the arm to produce local irritation, hives. He repeated these experiments with many possible causative agents, finding that only the pollen caused reactions. Persons who were not subject to hay fever did not respond even when grass pollen was used.

Blackley covered little glass slides with a thin layer of vaseline, placing them outdoors at exactly the level of his nose. After leaving them exposed through the day he examined, with his microscope, the deposits from the air which had settled on them. He found grass pollen there, but only when he was having hay fever. When his symptoms were worst there was most pollen on the slides.

Someone might argue that there is little grass in the centre of London or Manchester, but Blackley knew that pollen might be there even though the grass was far away. He sent up box kites containing the same little glass slides, to determine the distribution of pollen in the air and to gain some knowledge as to how far it might be carried. The results showed him that pollen is present in appreciable abundance as high as two thousand feet.

Blackley certainly had convincing evidence that pollen causes hay fever. Dr. Hyde Salter had written a book on asthma in which he stated that some persons may respond to exposure to cats with symptoms of asthma or hay fever. Blackley would have none of it. The cause must be pollen. The cat must have walked in the fields, becoming covered with pollen, which was brought into the house on its fur. When pressed with the argument that city cats which may not get to the timothy fields will cause symptoms, he replied that field mice had been covered with pollen, the cats had eaten the mice, thus getting pollen on their fur, and had then brought it into the house. To-day we realize that hay fever and asthma may be caused by many agencies, including pollen and animal furs.

The Weak Point in the Argument

One might think that Blackley's discovery would have been recognized at once as of great importance and that it would have excited as much enthusiasm as Von Behring's antitoxin. It did nothing of the kind. It caused scarcely a ripple of interest. There were still many doubting Thomases. Besides, in view of the knowledge of the day, it did not seem to make sense. If grass pollen caused hay fever, then all who were exposed to this pollen should develop the disease. But most persons did not. The only answer to this criticism was to call in the term *idiosyncrasy*, 'a reaction peculiar to the individual.' But no one knew what an idiosyncrasy was or why it was. Antagonists of the pollen theory insisted that it was merely a subterfuge to conceal ignorance. Idiosyncrasy just meant that there was something we didn't know about. They gleefully pointed out that this applied to the entire subject of pollens and hay fever.

There was another reason for lack of interest. Granted that Blackley and Wyman might be right, what could one do about it? Hay-fever victims had already discovered that a sojourn in the mountains or at the seashore gave reasonable relief. This was the way of escape for those who could afford it, and the two doctors had nothing new to offer in treatment. Further progress had perforce to await some new concept in medicine which might provide a logical explanation for what appeared to be the weak point in Blackley's thesis. This new concept was at last provided in the final decade of the nineteenth century, in the work on toxins which I have already described.

An Attempt to Make an Antitoxin

Sewall had discovered that animals may produce toxins. Roux had proved that certain bacteria do likewise. Ehrlich had found toxins in plants. In spite of vigorous efforts, especially by the German investigators, no germ had been found as a cause of hay fever. What was more natural, at a time when toxins were in vogue, than an effort to discover plant-made toxins in pollens?

Dr. W. P. Dunbar, of Hamburg, Germany, knew of Blackley's convincing work. He knew also the criticisms that had been raised, but he was convinced that pollen was in some way responsible for hay fever. To explain the fact that not all persons were affected he adopted the idea of an individual predisposition. This did not mean a great deal. It implied an analogy with other observed phenomena, such as food idiosyncrasy and drug idiosyncrasy, but it did not explain idiosyncrasy. It did not tell why some persons react differently from others. Dunbar decided that he must find, in the pollen, some agent which will affect only certain persons predisposed to

injury therefrom. So he spent several fruitless years trying to find a germ.

Finding no germ in pollen, he undertook chemical studies. He discovered an albumin or protein which seemed to be poisonous only to hay-fever sufferers. Dunbar concluded that it must be a toxin so, like Calmette and Von Behring, he set to work to immunize horses, this time against grass pollen. He believed that the resulting serum contained an antitoxin, named it pollantin, and sprayed it into the noses of hay-fever sufferers.

Although pollantin was widely acclaimed as a great discovery, it did not relieve hay fever. We now know that the substance in the pollen grains which appeared harmful for hay feverites was not a toxin, so no curative antitoxin could be produced.

Some persons were actually made worse after using pollantin sprays for some time. Dunbar himself was in this group. He explained the phenomenon quite correctly as the result of having developed an idiosyncrasy to horse serum. We see, then, a local allergic response in the nose comparable to the severe constitutional reactions to diphtheria antitoxin. Being due to surface application on the nasal membranes rather than hypodermic injection, it was much less severe.

In Summary

This brings us to the opening of the twentieth century. Up to that time the medical profession had not recognized the pathologic entity which we term allergy. The diseases which we now call allergic all seem to have existed from earliest times, but until the nineteenth century there was no suspicion of a relationship between such dissimilar maladies. The only available explanation for those cases in which there appeared to be a cause such as pollen, furs, flowers or foods was the term idiosyncrasy. This was merely a label, not an explanation.

Nevertheless, the final discovery could not have been made had it not been for the groundwork laid in earlier times. An adequate understanding of allergy would be impossible without knowledge of its antecedent background.

PART TWO

THEN CAME ALLERGY

Chapter VII

SOMETHING NEW AND SOMETHING STRANGE

"BUT, MY DEAR PORTIER, THE FACTS ARE AS I HAVE STATED. I HAVE repeated the experiments many times. When they did not turn out as I anticipated I believed I must have made some error. When again and again, in spite of adequate controls, these curious results were obtained, I was forced to realize that I was observing something quite new and altogether different from anything in my past experience."

The year was 1901. The speaker was Charles Richet, professor of physiology at the University of Paris, and he was arguing with his colleague, Dr. Portier. Richet, like Von Behring and Dunbar, was studying toxins. He had commenced his work two or three years before, while voyaging with the Prince of Monaco on the latter's yacht. The prince was a great scientist, one of the leading oceanographers of his time. With his encouragement Richet, always active and ever inquisitive, could not resist the opportunity afforded by the trip to study the urticating principle of the Portuguese man-of-war. In less academic terms, he wanted to know whether hives produced by the stinging nettle or jellyfish is due to a toxin.

The work was by no means completed on his return to France, so Richet continued it, using the sea anemone instead of the man-of-war. He made extracts, injecting them into dogs. When he gave large doses the dogs became ill. They had no symptoms from small amounts. He established the dose below which the dogs remained free from symptoms. He also discovered that dose which always caused severe or fatal symptoms. Intermediary doses produced symptoms of varying severity.

If the toxin theory, when applied to the jellyfish, was correct, then he should be able to start injections with small doses too minute to cause symptoms, and, gradually increasing the amount, immunize the animals. After that a dose normally large enough to cause serious illness would be quite harmless.

In the course of his studies something happened which was so

strange that Richet lost interest in his original objective. Here was something far more intriguing.

The dogs, instead of acquiring protection, became extremely ill after the second or third injection. Although the material injected did not change, something seemed to have happened to the animal in the interval between injections. The previously harmless material was now highly poisonous. And it was poisonous in the same dose or in even smaller doses than those which the dog had previously received without ill effects. Instead of conferring protection, the injections appeared to take away protection. This assuredly was quite different from past experiences with toxins. Richet found that the first injection never caused these curious reactions, but that they always occurred after a second or a later injection.

Portier, the sceptic, was asked to watch one of these strange occurrences. Together they studied the notes of the work on a dog named Neptune. Three weeks previously, Neptune, an otherwise normal animal, had received a small injection of anemone extract, which had scarcely bothered him. After a few days of apparent slight indisposition he had been as frisky as ever. He was frisky when the two doctors examined him. Dr. Richet gave Neptune a second injection, no larger than the first. Neptune at once became violently ill, and in twenty-five minutes was dead. Portier was convinced that he had witnessed something new.

What strange change had followed the first injection? What made an almost harmless substance intensely poisonous? Since the material was the same, the animal must have changed. Richet and Portier worked day and night on this tantalizing problem. Some dogs were injected every day, others once or twice weekly, and still other dogs received injections at longer intervals. The strength of the injection was altered, sometimes strong, sometimes weak, but the material used was unchanged.

After a year of such painstaking and self-critical investigation as only trained scientists are capable of, Richet and Portier made their preliminary report. The year 1902, the year of this report, dates the beginning of our understanding of allergy.

Three more years were to elapse before proof was forthcoming that this curious laboratory phenomenon had anything to do with human disease, and yet another year before the word *allergy* was coined by Von Pirquet.

In their preliminary report Richet and Portier reached two definite conclusions. *First*, a substance which may be practically harmless on first injection may act as a most powerful poison on a subsequent injection. *Second*, an interval must elapse between the two injections. This second point is of equal importance with the first. Dogs receiving injections every day or twice weekly or even once weekly escaped trouble. The interval between the first or preparatory injection and the second or shocking dose must be at

least ten days. It is interesting to recall that this is the same interval as the incubation period for typhoid fever (page 32).

At this stage Richet believed that the injected material must normally be slightly poisonous. He may still have been thinking of toxins. Certainly he recalled that contact with the sea anemone produces hives. So he proposed a theory. The normal body has some mechanism by which it protects itself against a mildly poisonous substance such as sea anemone. If, however, this substance be injected through the skin, the mechanism of natural protection is altered or destroyed. With later injections the irritating substance becomes much more powerful. To this phenomenon he gave the word *anaphylaxis.*

Prophylaxis was much in vogue at the time. Meaning 'favouring protection,' it was widely used, as it is to-day, in discussions of prophylactic or preventive vaccination against infectious disease. Neptune's tissues appeared to have experienced the reverse of prophylaxis. *Anaphylaxis* means a 'lifting up of' or 'removal of protection.'

But Richet was not yet satisfied. Could it be that completely non-irritating substances might do likewise ?

His colleague, Dr. Maurice Arthus, set out to answer this question. Where might one find some organic substance, some animal or vegetable material, which is incontrovertibly non-irritating, non-toxic ? Certainly blood serum itself, coursing through all parts of the body and indispensable for life, could not under any possibility be considered toxic. Arthus repeated Richet's experiments, injecting horse serum into rabbits. He found that successive injections of serum, at proper intervals, caused anaphylaxis.

This was rather a jolt for Richet's theory of removal of protection. One scarcely needs protection against something which is altogether harmless. For this reason Dr. Clemens von Pirquet, a young Austrian who subsequently became a world-renowned pediatrist, suggested the term *allergy* as preferable to anaphylaxis. Allergy means 'an altered capacity to react,' or 'altered reactivity.' It describes the phenomenon but makes no attempt to explain it. This was the trouble with Richet's 'anaphylaxis.' The logic of the term depended upon a theory. If the theory was not true, the term was illogical. In any event, the dog and the rabbit both experienced some change in their ability to react to sea anemone or horse serum during the interval between the first and later injections.

Resemblance to Human Disease

As a child specialist Pirquet had treated many cases of diphtheria. He was well acquainted with serum disease. He and his associate, Dr. Bela Schick, now a prominent New York pediatrician, recognized the similarity between experimental anaphylaxis and the unusual phenomenon of serum disease. In 1905 they published

their famous monograph on serum sickness, describing their reasons for believing this to be an anaphylactic disease. For the first time it was suggested that a human disease might depend upon some mechanism similar to that curious laboratory reaction known as anaphylaxis.

We can now understand why the explosive form of allergy was recognized first. Even the material used, horse serum, was the same both in humans and in the experimental animals, and in both instances the reactions were fulminating.

We can also understand why hives was soon suspected of being an anaphylactic disturbance, since this is one of the prominent symptoms of serum disease. Several investigators soon suspected other human diseases, especially hay fever, as being allergic, but four or five more years were to elapse before proof was forthcoming.

When Richet and Portier were watching the death agonies of Neptune they realized that they were observing a startling, new, previously unknown phenomenon which might have great importance in medicine. I doubt if they realized that Richet's investigations were destined to make him one of the great men of all time in medicine, one with Harvey, Jenner, Pasteur and Ehrlich, as a founder of a new division of the medical sciences. Nor did they know then that within a few short years Charles Richet would receive the great Nobel prize in recognition of his remarkable discovery.

In Richet's case luck played a most insignificant part. The attribute that characterized the man more than all others was inquisitiveness. Always he wished to know the answer, especially when the answer was unknown. Even on his holiday he must learn why the jellyfish stings. When, in searching for this answer, he chanced on another riddle, he could not rest until he had discovered the explanation. Others before him had seen similar phenomena. Many doctors had observed reactions to diphtheria antitoxin, but they had merely described them as idiosyncrasy and let it go at that. This was not enough for Richet. He felt driven to pry deeper into the mystery. It was his refusal to accept an unsatisfactory explanation that made him a great man. Others had had the opportunity. He took advantage of it.

Even after his retirement Richet's inquisitiveness continued to plague him. He took up study of the occult. He visited mediums. He became versed in the lore of their profession. It is said that what he wanted most was to procure a specimen of 'ectoplasm' so that he might examine it under the microscope. This, of course, he never accomplished.

Chapter VIII

WHEN SUPPOSED FRIENDS BECOME ENEMIES

WHEN ONE IS ILL MEDICINE IS PRESCRIBED. TAKE SUCH A SIMPLE DRUG as aspirin as an example. Anyone knows that it will relieve headaches or other mild pains, and will help to break a fever. The public has become so accustomed to purchasing it for a small charge in any chemist's or department store that some mildly resent a doctor's prescribing it. One patient's attitude was, "He might as well have ordered sugar pills. If it was aspirin that I needed I would have bought it myself. Maybe he thinks I should go to him for a prescription when I want to buy a laxative !"

Allergy to Drugs

Aspirin does not affect all persons alike. Some there are who react in an altered manner. The number who have hives caused by aspirin is not inconsiderable. They usually do not suspect the drug because they feel that medicine should relieve symptoms, not cause them. Even those who have discovered that their urticaria, angioneurotic œdema, hay fever, or asthma has been due to aspirin, may find difficulty in avoiding it. The drug is widely used as a constituent of proprietary pills and powders, advertised under trade names which contain no suggestion as to contents, and guaranteed to relieve this or that ailment.

Although sensitization to aspirin is one of the commonest drug allergies, only a few persons are so exquisitely sensitized that they have alarming symptoms after taking the medicine. A few do get into as much difficulty as did Caroline. There have been anaphylactic deaths from a single aspirin tablet. Let us glance at a series of true instances occurring at a drug-stores fountain in America, where the 'soda jerker,' not even a registered pharmacist, can hand tablets across the counter in any requested quantity, even down to just one tablet.

The first nine subjects in our list ask for two tablets. They take both at once, probably with the idea that if one is good two should be doubly beneficial. Within twenty minutes all have such violent asthma that they can only sit and gasp. Three also have hives.

The tenth case knows that she cannot take aspirin, but she is wheezing badly for she has eaten something to which she is allergic. A friend suggests aspirin for relief, but she refuses. So a tablet with another name is proffered. Unfortunately, it is but a proprietary name for pure aspirin. Three minutes after swallowing it, our asthmatic lady lies dead.

Next in the line-up are three middle-aged persons with bad hearts. For one complaint or another each takes an aspirin tablet.

Within from thirty to forty minutes all have severe attacks of angina pectoris.

Then there is a fifty-five-year-old man. He has learned from experience that merely touching the lips with aspirin will induce an asthmatic attack and make him blue in the face within thirty seconds. This time his chemist friend gives him a powder. Neither knows that it contains aspirin. The result is anaphylactic shock, with our man hovering between life and death for five hours. Fortunately, he survives.

A man in his forties had had his tonsils removed, and his throat was mighty sore. A doctor friend standing near by thought he could fix it. He applied some powdered aspirin to the raw throat. The victim developed severe asthma, became blue from suffocation, and cried out, "My God, what did you give me?" After a time he recovered.

Not every person who insists that he cannot take aspirin is truly allergic to it. Some find that it makes the pulse unpleasantly rapid, and causes palpitation. Others find that it merely makes them nervous. This is not allergy. It is but a normal aspirin response, greatly exaggerated. Persons truly allergic to aspirin respond with the usual allergic symptoms (page 14).

One person or another may be allergic to almost any of the drugs in use to-day, both those derived from plants and those, such as aspirin, which are made synthetically in the chemical laboratory. Three symptoms, uncommon in allergy due to other causes, are rather frequent in drug allergy. They are fever, special skin eruptions, and changes in the blood, particularly damage to the white blood cells and to the blood platelets.

The Side-chain Theory Explains Allergy

The recognition of drug idiosyncrasy as an allergic reaction was the first major advance after the fundamental facts of allergy had been recognized and serum disease had been called allergic. But we must study these fundamental facts in more detail before we can understand how such harmless, helpful substances as medicines can cause allergic trouble, even though they be taken by mouth rather than hypodermically, as was the case with horse serum, antitoxin, and anemone extract.

After the splendid start had been made by Richet many of the keenest minds in medical research turned their attention to the elucidation of this baffling problem. It became apparent that only certain types of materials carried into the body could cause allergy. Foreign protein was the one chemical which did it consistently.

Protein represents the living part of the cell, be it vegetable or animal. Every species in both kingdoms has a different protein. The more closely related the animals or plants the more nearly alike are their proteins, but they are never identical, except within the species. Chemically, monkey protein is more nearly the same

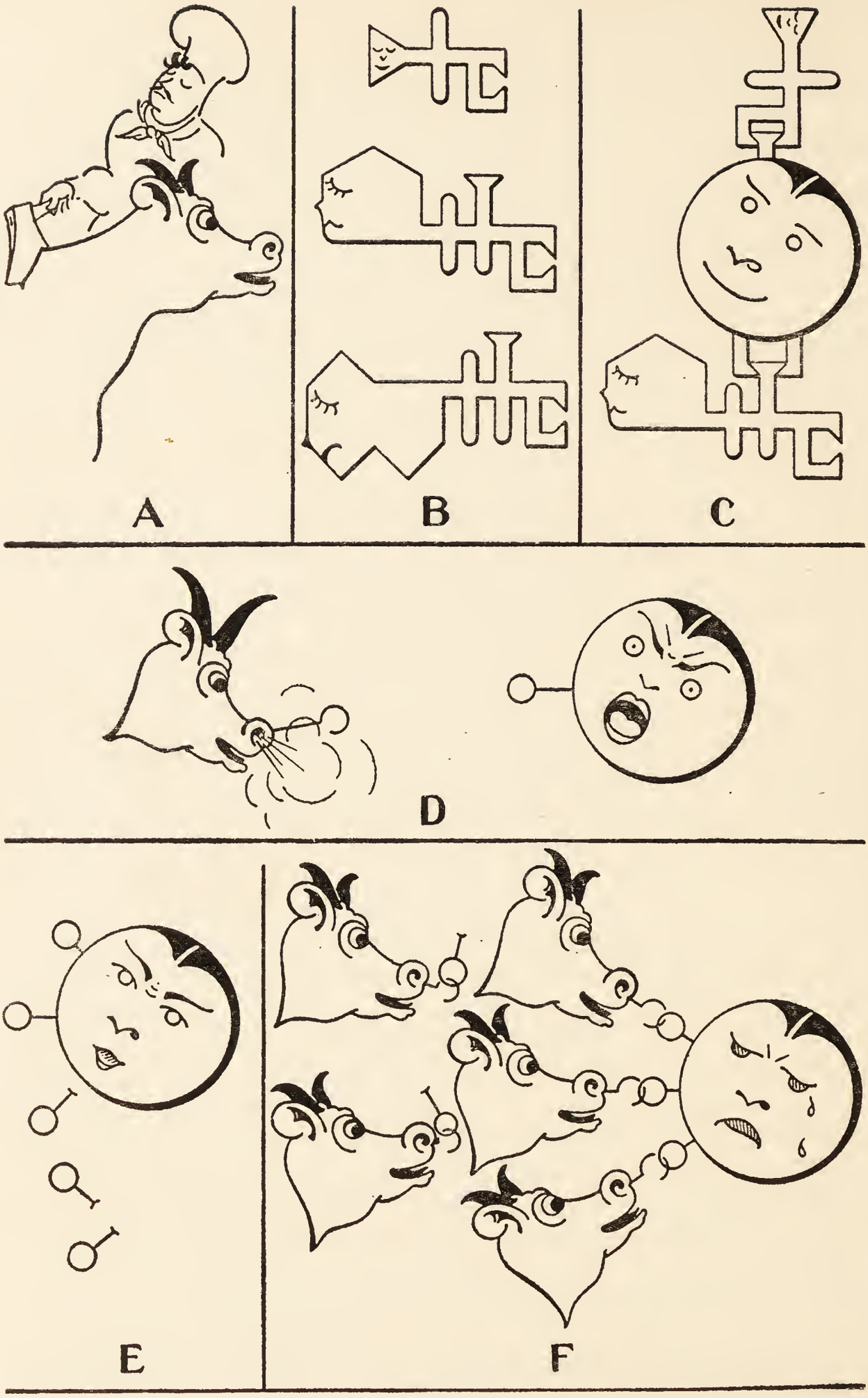

FIG. 6

NORMAL DIGESTION AND THE PROCESS OF SENSITIZATION TO FOODS

as human protein than is beef or lion protein, but there is a difference. Although the proteins of different species of birds are all different, they resemble each other more than they do those of members of the cat family, for example. Pea and bean proteins, although not identical, are more nearly alike than are pea and cabbage proteins.

The basic elements which make up proteins are a group of chemical compounds called amino acids (see Fig. 1). Although there are but twenty-two of them, variation in the manner and sequence of their number and arrangement in each of the protein molecules provides an almost limitless number of combinations. This is analogous to the limitless number of words that may be made from the twenty-six letters of the alphabet.

Every living thing seems to be more or less an enemy of every other living thing. With the exception of a few animals, particularly man, this enmity is not exaggerated among members of the same species. Dogs usually get along reasonably well together. So do cats. But cats and dogs mixed do very poorly, indeed. In allergy it would appear that this antagonism extends even to the chemical relationship between proteins of different species of plants and animals. Beef protein or egg protein is taken into the human stomach during the normal process of eating. Digestion breaks it up, separating the amino acids from each other. These are absorbed into the blood and carried to the body cells, there to be used, as needed, for replacements necessitated by the wear and tear on human protein. Normally, egg protein and beef protein do not enter the blood undigested. When they do so they injure body cells just as we have seen bacteria do (page 33), and call forth a similar protective response.

Protein Sensitization

The early investigative work indicated that for a substance to produce allergy it must be protein. The injection of amino acids,

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FIG. 6

NORMAL DIGESTION AND THE PROCESS OF SENSITIZATION TO FOODS

In the normal process of digestion (A) beef protein is broken up by the digestive enzymes into its constituent amino acids, in the intestinal tract. These (B) are absorbed into the blood and carried to the body cells which (C) draw them into their structure as replacements for damaged or discarded amino acids. The process is similar to that of repair of a damaged locomotive, with new boiler plates, rivets, etc., so that it may continue to work properly.

Quite a different situation develops if for some reason undigested beef protein is absorbed, getting into the blood stream. Here (D) we have the same situation as with typhoid-bacillus protein (Fig. 4). There is cell damage with consequent production of protective antibodies (E).

If at some later time undigested beef protein again enters the body and there are not enough protective floating antibodies, the beef protein molecule will become attached to human cell proteins, damaging the latter. Protection is not adequate (F). Apparently protection against a harmless food has been removed or destroyed. The condition is termed anaphylaxis or allergy.

sugars, fats, and even partially digested proteins failed to produce the anaphylactic state.

From his early investigations Victor Vaughan concluded in 1907 that immunity and allergy are different manifestations of the same fundamental response of body cells, caused by contact with harmful foreign protein. This idea was promptly accepted by other investigators. If this is true one should be able to explain allergy in terms of the Ehrlich side-chain theory. Remember that the living protein of the body cell, injured by direct contact with a foreign protein, living or dead (the protein of another species), protects itself by making antibodies. These antibodies attached to the cell proteins are produced so abundantly that many become loose, circulating freely, and defend the living protein thereafter by combining with and neutralizing the activity of the foreign protein before it can reach the living cell. This is immunity.

Now suppose something were to happen to the mechanism of antibody production so that the antibodies are no longer shed, but remain attached to the cell. Normal antibodies at maturity are loosened from their attachment to the protein very much as ripe apples drop from the tree. But if for some reason this process of maturation stops before shedding, the situation is fraught with dire possibilities. If the antibodies remain attached or 'sessile,' and there are not sufficient free antibodies to combine with and neutralize the foreign protein or antigen when it arrives, attachment will be made directly to the human cell protein by means of the sessile antibodies, with consequent serious damage to the protein. This, according to the theory, is what might well be happening in allergy.

I am once again in my garden, throwing sticks to the dog, keeping him amused and protecting myself. At long last comes the bear. He comes at me. I protect myself with a shovel. The bear is quite pleased with the shovel, and I realize that now I must make many shovels. When later the bear again shows up I have a nice protective shovel in my hand. The bear comes for it. He grabs it. But something is wrong. I have a cramp in my hand or for some reason I cannot let the shovel go. The final outcome is very damaging to me.

We may therefore look upon the allergic state as dependent upon the same fundamental processes as those active in immunity or protection. For some reason not yet understood something goes wrong with the orderly process of protection, as a consequence of which, instead, there develops increased susceptibility.

Some of you may have difficulty in imagining how anything as small and apparently simple as a single cell can undertake such complicated chemical procedures. A cell even when enlarged nine hundred times through the lenses of a microscope appears little larger than a pinhead. To-day, when we speak of macrocosms and microcosms and have been taught to understand the tremendous

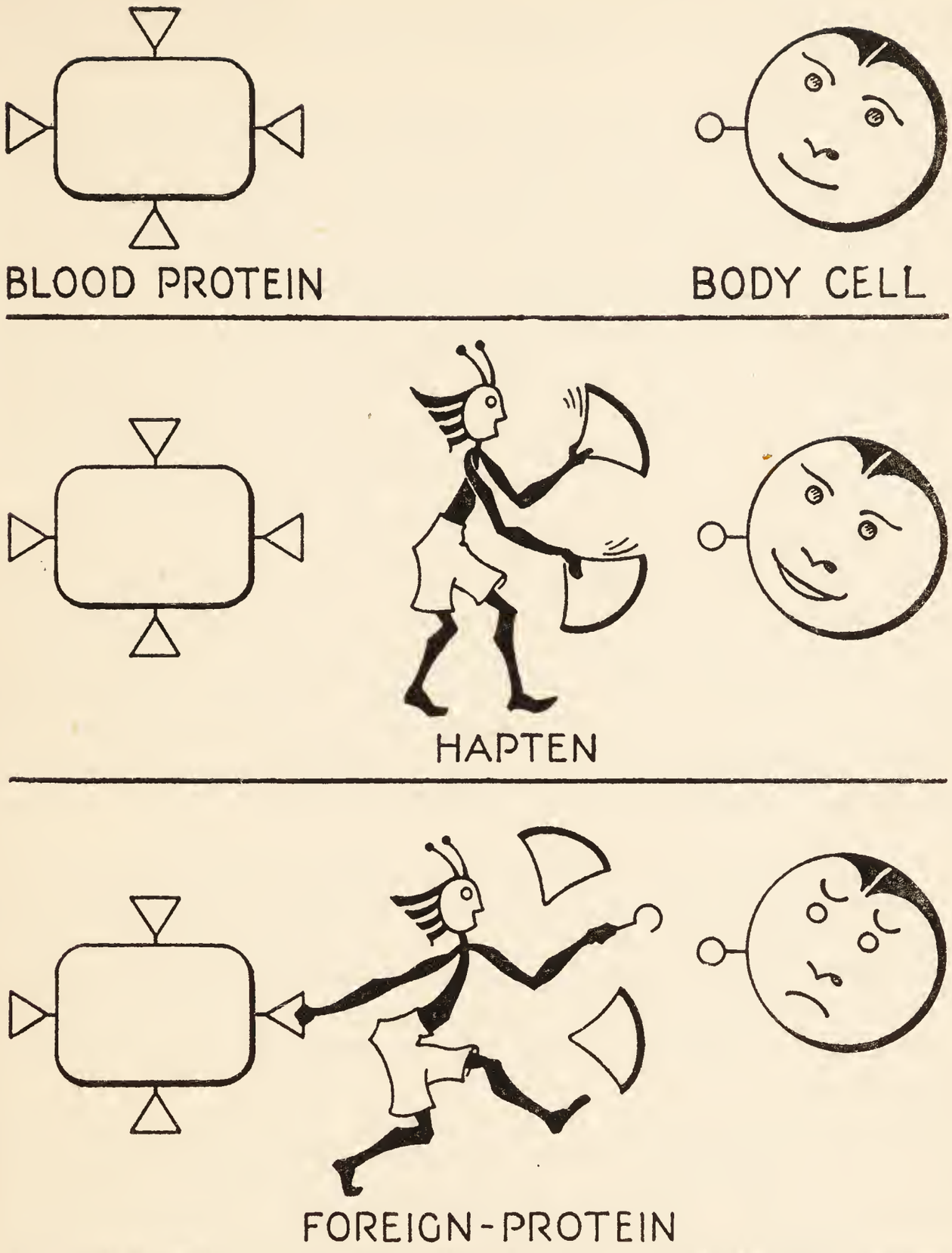

FIG. 7

DRUG ALLERGY

There are several kinds of protein in the animal body. They are all human protein in that they differ from the protein of the blood of other animals, but even so they are not all exactly like the living cell protein. Blood protein, manufactured by the living cells, is not alive.

We give drugs (middle panel) to heal diseased tissues, to make cells work more smoothly. A drug may become allergenic by combining chemically with inanimate protein in the blood or tissues, producing (lower panel) a new chemical which reacts like a foreign protein.

activity going on among the constituents of a single atom, we should have no difficulty in imagining far more complicated activities in the protein molecule made up, as it often is, of hundreds or thousands of atoms.

When we think of the lowly amoeba, one of the simplest forms of life, consisting of but a single cell, which digests the food that is available in its immediate neighbourhood, builds it into its own structure, excretes its waste products, and after this still has energy to spare for movement, growth and reproduction, we must realize what a complicated mechanism the cell is.

Victor Vaughan wrote 'living cells are capable of being trained or educated. In other words, their behaviour may be modified by changed environment.' Foreign protein in the neighbourhood of a cell constitutes a change in its environment. The cells must adjust themselves to compensate for this change.

There are a few more technical terms which we should know. Although antigen is used in the same sense as in immunity, the word allergen is more frequently applied to those antigens which cause allergic symptoms. An allergen is the substance which produces allergy. The process of becoming allergic to an allergen is spoken of as sensitization. I am allergic to eggs because I have become sensitized to the egg allergen. My cells must have antibodies to egg protein. There are other terms in the vocabulary of the allergist, but these will suffice for our needs.

Drug Hapten Plus Human Protein Equals Foreign Protein

When everything was going along merrily with the concept of protein sensitization someone threw in a monkey wrench by pointing out that typical allergic responses, with all the classical symptoms, could be produced by many drugs such as iodine, iodoform, and quinine, chemicals which have nothing in the world to do with protein.

Scientists came to the rescue, as usual. A German doctor suggested that these foreign chemicals, after entering the body, combine with normal human blood protein. This is not the protein of the living cell, but another human protein, not alive, which is dissolved in the blood. It is not a protein which is foreign to the body. The close chemical combination between blood protein and the drug results in a new combination which then acts as a foreign protein. This has since been proven by the careful research of Dr. Karl Landsteiner, a Viennese physician now living in New York. For this and especially for his equally important work on blood groups, which does not interest us here, he, like Richet, received the Nobel award.

A drug or other substance which becomes combined chemically with a protein, thus forming a new, more complex protein which is immunologically different from the original protein, is called a hapten.

Chapter IX

ON HANDLING OLD FAMILIAR OBJECTS

A MODERN BOY, ASKED TO DEFINE THE EXPRESSION 'TO BE ALLERGIC to,' would probably say, 'antagonistic to,' 'don't like,' or 'can't stand.' As definitions go, these are not bad. The lad probably derived his understanding from a remark of the movie queen or the heroine of a short story to the effect that she was allergic to the villain.

Although the term has had over a third of a century of existence, only during the past ten years has it been widely used by the public. To-day, nearly everyone has at least a hazy understanding of its significance. At times, it is quite hazy indeed. A patient who certainly should have absorbed enough understanding to know better once wrote for another bottle of desensitizing extract, saying, 'I have used up all of my allergy. Please send me some more.'

Patients often regale their doctors with most unusual stories of their allergic reactions. While some are true as described, others are distorted, due to misinterpretation. A lady with intermittent attacks of asthma once asked whether the condition was 'catching.' She took vigorous exception to the assurance that it was not contagious. Insisting that she had clear proof, she said that every time she wheezed her parrot also wheezed. I don't know that she ever did accept the explanation that the old bird was just up to his customary trick of imitation.

When an allergic patient gives a curious story or mentions an unusual suspicion as to the cause of his symptoms a wise doctor will not categorically deny the possibility. Too often have I exercised what I believed was my good judgment in denying the rationality of the patient's claim, only to admit later that he was right.

A young lady complained that she was allergic to her bedroom furniture. She had a disfiguring eczema of the lower half of the face and of the exposed V-shaped area of the neck. This is the region frequently involved in allergy to cosmetics, and when she was found to be sensitized to orris root she was told to keep and enjoy her new furniture, but to procure cosmetics which do not contain orris root.

Three weeks later she was only slightly improved and still insisted that the furniture was responsible for her difficulties. She had used the same brand of cosmetics for years, and had no trouble until two weeks after purchasing the furniture. Her eczema was always worse when she spent much time in her bedroom, and was relieved in some measure when she slept elsewhere.

On her next visit she had the drawer of the bedside table tucked

under her arm. Scrapings were made of the wood, the glue and the lacquered front of the drawer. These bits of material were placed on her forearm, covered with squares of cellophane, and sealed with adhesive. Two days later, when these patch tests were removed, there was a little spot of eczema where the scrapings from the lacquer had been applied. Our lady had a lacquer dermatitis similar to that which had affected the hands of so many persons during the recent mah-jong craze. Chinese lacquer is especially likely to cause sensitization.

For confirmation some of the original lacquer obtained from the furniture manufacturer was applied. This being positive, the young lady disposed of her bedroom furniture.

A year later she had the same dermatitis of the face and neck in more aggravated form. In the interval she had improved, but had not cleared up entirely. Then the condition had become worse. As we sat talking, I became fascinated with the redness of her fingernails. I did not recall having observed this colour predilection at the time of our first conference. I noticed that she was in the habit of stroking her face and neck. We patch tested her with her nail polish. The resulting reaction was strongly positive. She discontinued the polish, and within three weeks her skin was without blemish.

Searching for any possible connection between the two experiences, we discovered that over-supplies of lacquer not used by furniture manufacturers are purchased by cosmetic makers for use in liquid nail enamel.

The Evil Touch

Eczema or dermatitis caused by contact with allergens is easily controlled if the cause can be discovered and avoided. Either of these provisos may be difficult of execution. Nickel, for example, is a frequent cause of contact dermatitis and usually easily recognizable. Since it is so widely used one may have trouble in avoiding it. A lady had a patch of eczema on the left wrist, directly under her white-gold watch. The nickel test was positive, and she was advised that since there is nickel in so-called white gold, she should carry her watch in her pocket book or pinned to her dress. Her dermatitis cleared up, but a few weeks later she developed a ring of eczema on the base of the right thumb. She had been sewing, and the ring represented the imprint of the scissors handle.

The most pronounced example of nickel dermatitis I have heard of was a lady who would develop a small patch of eczema whenever and wherever she was given any medicine with a hypodermic needle. Even the scratch of a needle would cause a reaction. Here, even though the duration of contact was never more than a few seconds, symptoms appeared.

Nickel is the most highly allergenic metal. From 40 to 100 per

cent of workers in the Swiss nickel industries develop nickel sensitization.

The difficulty of continuous avoidance is illustrated in two cases of leather dermatitis. A man had eczema of the forehead, which was promptly proven by patch test to be due to sensitization to his leather hatband. Substitution of a silk band cured the condition, but the following spring it returned, this time on the hands. Even though he was a physician, several weeks elapsed before he realized that the recurrence was due to the leather grips of his golf clubs. After these were wrapped in adhesive he had no further trouble.

The second man had eczema of the left palm. After prolonged search he found the cause in a leather handgrip which he had strapped on the steering-wheel of his car. Discarding the grip, he cured his dermatitis, but a few months later it returned on the fingers of his right hand. Although he suspected some contact with leather, weeks passed before he noticed that he was carrying his keys in a leather folder in his right trouser pocket, and that much of the time his hand was in his pocket.

Dermatitis on the thigh may be due to carrying matches in one's trousers pocket.

Also Foods

There are two general types of allergic eczema. The first, contact dermatitis, is illustrated in the above examples. It involves exposed areas of the skin or areas where direct contact with the allergen may occur. The woman with dermatitis from a rubber girdle has it not in an exposed area but in a region where contact is direct. The hands, face or ankles are more frequently involved. When acute and severe, contact dermatitis may take the form of weeping eczema.

The second general type involves the face and flexor surfaces, the neck, the front or bend of the elbow, the inner aspect of the wrist, the groin and behind the knees. It rarely weeps. This form is usually due to sensitization to substances which reach the skin from inside, carried to it through the blood. It is due chiefly to foods, less often to inhaled substances such as house dust, dust from feathers, silk, and the like.

How and Why

It appears as though in each chapter of this book we must correct statements made in preceding chapters. This corresponds to the successive changes in the interpretation of allergy that scientists have had to make as we have learned more of the disease. In the last chapter we saw that, although, according to the original theory, allergens must be protein, drugs are also potential sensitizers. To keep the theory consistent the idea was developed that a combination of the drug with human blood protein may produce a new sensitizing protein.

In discussing contact allergy we must make still more modifications. Poison ivy will cause a skin reaction only where it comes in contact with the skin. A person allergic to ivy may drink a weak extract of the plant without getting into difficulties. According to the theory this should give him much more trouble, since absorption from the stomach or intestines would enable the ivy chemical to combine, like a drug hapten, with blood protein. Instead, ivy, nickel and other contact allergens cause reaction only in those cells of the skin with which they come in direct contact. The blood and its special protein appear to play no part whatsoever.

Of course, one could rig up a theory that the combination of allergen with body protein in order to form a new protein would be with the proteins of the skin cells themselves. But this would be stretching the idea pretty far, and there has as yet been no proof that this occurs. It would be better logic, at least until we know more about it, to discard the tenet that allergens must be protein. Many substances which are not protein may cause sensitization. This is especially true in contact allergy. Mention of but a few of the many contact allergic excitants will give some idea of the wide diversity of possible trouble makers : poison ivy, tulip bulbs, adhesive plaster, corn-starch, chrysanthemum leaves, sawdust, newspapers, cleansing tissues, sanitary napkins, house dust, feathers, furs, clothing, ointments and other medicines for local application, hair tonics, shoe polish, clothing dyes, dress shields, rubber, plastics, cosmetics, soaps, earphones, silk, wool, etc. None of these will cause trouble unless the individual happens to become sensitized to them.

Allergy to Husbands

Speaking of the cinema star and her allergy to the villain, doctors are often asked whether human beings may be allergic to each other. One hears tales of this sort, but finds them mighty hard to authenticate. Years ago I heard of a woman being allergic to her husband's perspiration. Since nothing could be done about it they were divorced. I was never able to locate the hero or heroine of this strange story. Quite recently I heard of a man and woman, not married, who often played as bridge partners. Although they were both charming people, an intense antagonism gradually developed. It was then found that she was allergic to his dandruff.

These are amusing stories, more or less, but that is all. They originated quite early in the evolution of allergy, when a Dutch physician thought he had shown that persons can become allergic to human hair and human dandruff. No other allergist has confirmed this theory, and we must pass it up for the present as not proven.

Although I have never seen a case of marital incompatibility due to sensitization of one party against the other, there have been instances where this appeared to be the case. A wife had asthma

only when her husband was near. Realizing this, she gradually developed an antagonism toward him such as you would have against oysters if you found that they always caused stomach-ache. She was found to be strongly allergic to chicken feathers. The husband was a bird fancier, spending much of his spare time in the chicken house. When he came home his clothing was thoroughly saturated with chicken-feather dust. This difficulty was easily rectified, and the divorce court lost the opportunity of settling a unique complaint.

Chapter X

THE SUN SHINES BRIGHT

ON A HOT JULY MORNING DR. SMITH WAS SEATED AT HIS DESK ENJOYING the cooling breezes of the electric fan. The telephone rang with that insistence which only a doctor's phone seems capable of transmitting. It was a hurry call to a lady living in the next block. She had been found unconscious on the sleeping porch. He started down the street at a dogtrot but soon slowed down. The hot midday sun was indeed scorching. A maid opened the door and hurried him upstairs. As they came into the glass-enclosed sleeping porch it seemed as though they were penetrating a wall of super-heated air.

On the floor near the inner wall lay a girl in her early twenties, small, dark and pretty. She wore no clothing. Dr. Smith sent the maid for a wrap and turned to examine his patient. Her condition seemed too serious for a simple fainting attack. He carried her into the cooler bedroom and with the maid's help applied cool damp cloths to her forehead. As he was still wondering what could have caused the attack, he observed a small blemish on her shoulder which, even as he looked, grew in size. Others soon appeared here and there. He now suspected the diagnosis. The evidence was enough, at least, to suggest the proper treatment. Adrenalin wouldn't produce a miracle as it had in Caroline's case, but it would help raise the blood pressure, and she was still badly shocked. Assuming that she was allergic to heat, the application of the opposite factor should produce quite rapid relief. The maid was sent for ice. Ignoring the puddles, the doctor rubbed the girl's arms, legs and chest vigorously with large chunks of ice. Improvement was rapid enough to be almost spectacular. The red blotches which had evolved into widespread urticaria faded quickly. Consciousness returned, and within thirty minutes the young lady was resting comfortably on another bed. As she told Dr. Smith of her past experiences he realized that his diagnosis had been correct, and that she had long known the nature of her trouble.

"I have understood for a number of years," she said, "that I

react to heat and sunlight in an abnormal way. As a girl I developed hives each year during the first hot days of summer. Then I would have no further trouble until midsummer, when I went with my parents to Atlantic City. I had no difficulty in the hotel, but when I would venture on the beach in a bathing suit or even walk along the boardwalk in a light summer dress I had hives almost from head to foot. I never could tolerate hot baths. Not only would they cause hives, but unless they were followed by a cold shower they would leave me feeling quite exhausted, blue, and depressed.

"A doctor tested me for allergy to heat and cold, and studied my response to ultra-violet rays. He found that I reacted to heat and sunlight. He explained that hives during the first heat of summer disappeared later, even though it became still hotter, because I had gradually acclimatized myself to the increase in temperature. The trouble at Atlantic City was in part heat but more particularly sunlight, to which I had not as a rule been adequately acclimatized. He explained how the proper treatment consisted of a programme of acclimatization and gave me directions for gradually increasing the temperature of my baths and to calisthenic exercises to increase my own body heat. I did very nicely after that, but this time I had an unusual degree of exposure.

"I had been straightening the books in the library, had got myself hot and dirty, and was on the point of stepping into a tub when the phone rang out on the sleeping porch. It was so hot that I didn't even slip on a gown. What I thought would be a very brief conversation lasted twenty minutes. When at last I hung up the receiver I felt faint and realized that I had given myself an enormous dose of heat and sunlight. I knew that cold water would relieve me, but I couldn't reach the bathtub."

Histamine, the Troublemaker

I have recorded the above episode in considerable detail because it illustrates so many phases of what we shall term physical allergy, an allergic type of response to certain physical factors, particularly heat, cold, sunlight and effort. If this is actually allergy, we must at last give up all pretence that protein must play a part in the reaction. Certainly one could not conceive of heat or sunlight combining with blood protein to form a new foreign protein. We must at last broaden our concept of allergy. The definition of the word need not be changed. One who is allergic reacts to a given stimulus, whether it be food that is eaten, pollens inhaled, drugs administered one way or another, cosmetics or clothing or even atmospheric environmental factors, in a manner which is altered from the normal. This changed reaction must still show its presence by those symptoms that we have come to recognize as allergic : sneezing, wheezing, a skin rash, headache, indigestion, abnormal fatigue or one of the other symptoms previously listed. Allergy is

then an altered response, as a consequence of which certain specific symptoms appear.

If we are to accept this broader understanding of the subject, must we now discard the Ehrlich side-chain theory? How can we still talk about antigens and the antibody response when dealing with such non-chemical conditions as heat and cold? There is much of which we are still ignorant as regards the mechanism of allergy, but we can still hold on to the side-chain theory, at least until something better is presented. In order to do this we must return briefly to the discussion of the basic processes which are at work.

When allergy was in its infancy the idea had been that antibodies combining with the foreign protein injured the latter, releasing a poison called the protein poison, which was present in all forms of protein. It was this poison, brought in from outside in the foreign protein, which caused symptoms. With acceptance of the theory of sessile or attached antibodies, it was realized that possible damage to the body cells would be of far greater importance to the individual than damage to the foreign protein.

Many early investigators had found out what happens in the body during anaphylactic shock. They would, for example, sensitize a guinea pig to the white of an egg by injecting this material under the skin or into a vein. After ten or more days they would inject egg white again. The pig would develop anaphylactic shock. At autopsy they found that a certain type of muscle known as smooth or involuntary muscle had gone into spasm. These muscles in the bronchi contract down so that the guinea pig cannot get air into or out of the lungs. It was the close resemblance of this bronchial constriction to what happens in human asthma that gave rise to the suggestion, in 1910, that asthma might be an allergic disease. Other smooth muscle, such as that of the uterus, also contracts. Another change in anaphylactic shock is increased permeability of the cells lining the capillaries, the smallest blood vessels. As a consequence fluid leaks out into the tissue spaces, causing swelling. This is what happens in hives and angioneurotic œdema and may be what happens in the brain during an attack of migraine. The loss of fluid from vessels explains allergic shock. The blood pressure falls to such a level that the heart is no longer able adequately to propel the blood. For the present we need not interest ourselves in other changes during the allergic reaction.

Shortly after the turn of the century, when anaphylaxis was a new subject and bacteriologists and immunologists were working feverishly in this promising field, a British physician, Henry Dale, was studying quite another problem. He was investigating the poisonous action of ergot, a fungus which grows on rye. It had long been known that rye bread contaminated with ergot may cause miscarriages. Extracts of ergot caused the muscles of the uterus

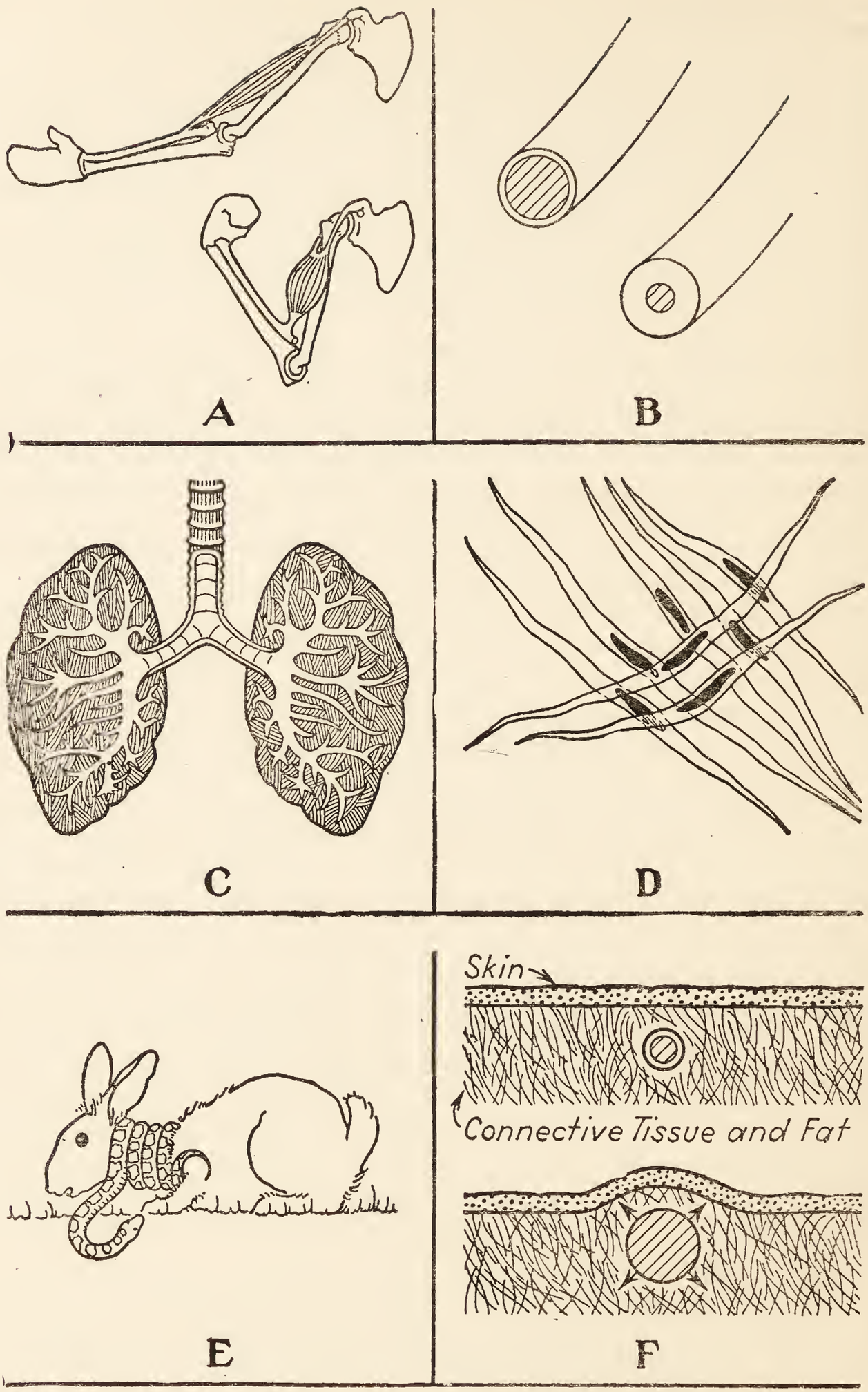

FIG. 8

CHARACTERISTIC ALLERGIC TISSUE RESPONSES

to tighten up, and physicians had used it for this purpose whenever the uterus did not contract as it should after childbirth. But it was a dangerous drug since it had other undesired effects.

Dr. Dale had found several poisons in ergot and was studying their effects on guinea pigs and other animals. One of these poisons was called histamine. Histamine caused the smooth muscle of the uterus to contract. When Dale learned of the findings of others in regard to anaphylactic shock he realized that all of these abnormal changes, smooth muscle spasm, increased capillary permeability and others which we have not mentioned, can be produced in precisely the same way by injections of histamine. Believing that the poison released in the allergic reaction might be histamine or some closely related substance, he turned to the study of allergy. In the course of time it was clearly proven that histamine may be produced during the destruction of protein, that it appears when cells are damaged and that when it is released in the body it can produce those changes which are responsible for allergic symptoms.

Dr. Dale contributed much to the histamine theory of allergy. As time went on he became Sir Henry Dale and the fifth among the brilliant scientists whom we have mentioned to receive the coveted Nobel award. Paul Ehrlich, Emil von Behring, Charles Richet, Karl Landsteiner and now Henry Dale.

It remained for another Englishman, Sir Thomas Lewis, to prove that in physical allergy, in the absence of an antigen-antibody

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FIG. 8

CHARACTERISTIC ALLERGIC TISSUE RESPONSES

Voluntary muscle, the type that is controlled by the will power, is attached to some bony or tendonous structure at each end so that when contracting it moves one of the harder parts of the body (A). The walls of blood vessels, stomach, intestines, the bronchi or air tubes in the lungs and other tubular structures inside the body, not controlled by the will, contain many muscle fibres. These muscles are not attached to bony structures, but to the small amount of connective tissue which separates the closely interwoven muscle fibres. Each fibre (D) is a single elongated spindle-shaped cell. In blood vessels or bronchi the fibres run both lengthwise and more especially in a circular distribution so that when they contract (B) they constrict the hollow tube, making it smaller, thicker and, incidentally, diminishing the diameter of the inner hollow space. The effect might be likened to the constricting action of a serpent (E). If a serpent were to constrict the neck, it would be more difficult to get air in and out of the lungs. In the bronchi it is not the muscles of the larger tubes which constrict, producing the symptoms of asthma, but those in the very small terminal bronchi deep within the lung (C).

The second and more important allergic response is that of decreased capillary resistance (F). In the upper portion of this figure we see a layer of skin beneath which is connective tissue. In the centre is a cross-section of a capillary, the smallest part of the blood vessel system, the connecting link between arteries and veins. There is no muscle in the capillary walls, the separation between blood and connective tissue being the thickness of but a single cell.

In the allergic reaction the capillary walls dilate (lower section) and the injured cells allow fluid to pass from the blood into the connective tissue. If this is near the skin there will be some visible swelling as occurs in urticaria, similar in appearance to the local reaction after a bee sting.

While there are certain other reactions, increased capillary permeability and smooth-muscle spasm are the two most characteristic allergic responses within the body.

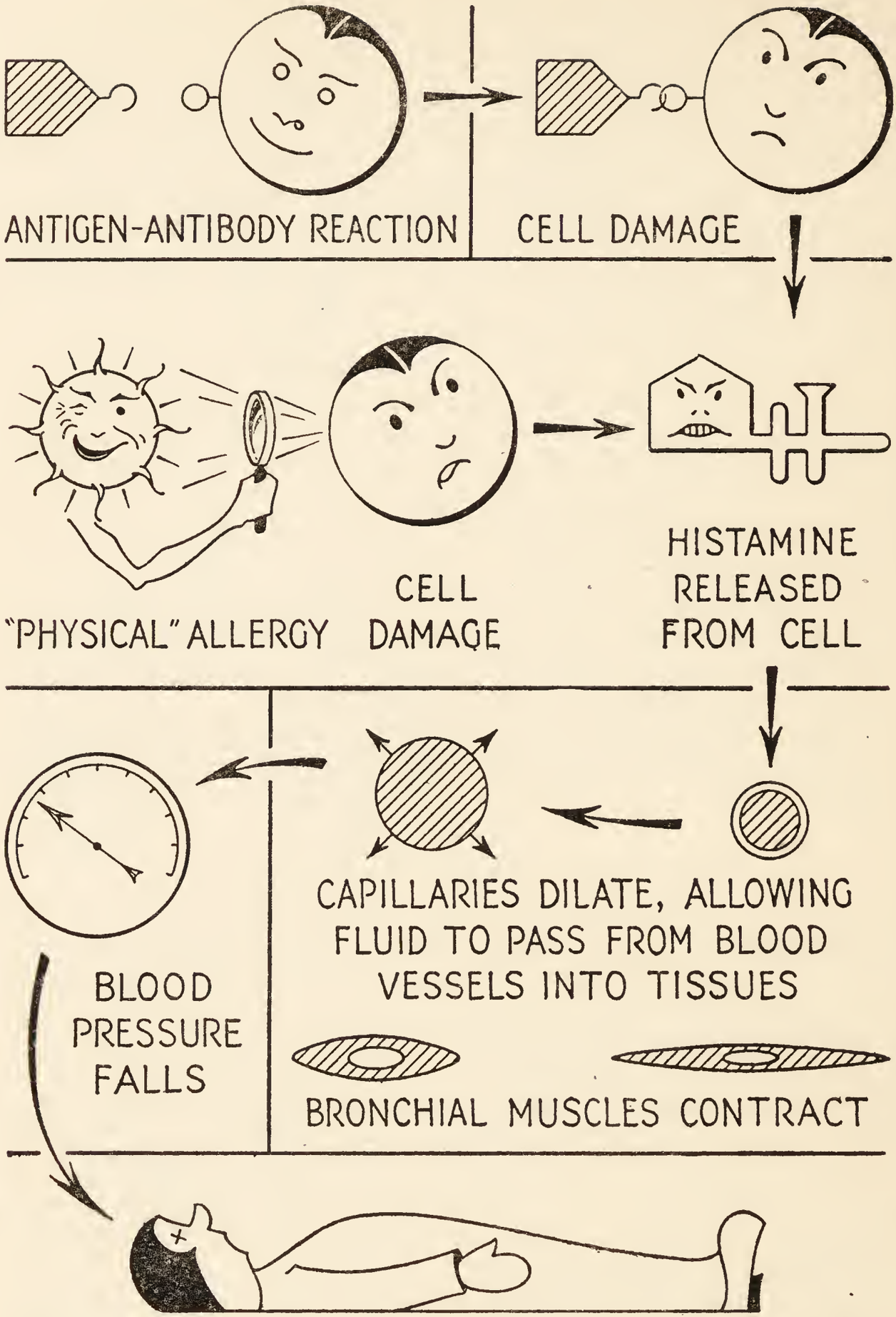

FIG. 9

HISTAMINE AND ANAPHYLACTIC SHOCK

reaction, histamine or a histamine-like substance may be released by normal body tissues. If the skin of a person allergic to heat be exposed to heat, some substance is released in the heated area, not elsewhere, which behaves like histamine. Finally Dr. Charles F. Code, an American who was awarded the Theobold Smith prize of the American Association for the Advancement of Science in 1938, perfected a method of testing for histamine. He finds it present in the blood when patients are having allergic reactions.

You will recall that protein allergens injure body cells because of their affinity toward attached receptors or antibodies. The injured cells produce histamine. The latter is in turn responsible for ensuing symptoms.

In physical allergy the antigen-antibody reaction need not play a part. For some reason the cells are hyper-irritable or hyper-reactive to the excitant. Whether this be heat, cold, sunlight or mechanical irritation, such as scratching, the cell releases histamine. In other words, physical as well as chemical factors may cause injured cells to manufacture histamine.

If normal skin is damaged by freezing at 20 degrees Fahrenheit, it produces histamine. In allergy to cold the temperature threshold for the release of histamine is changed. Normal body temperature is 98.6 degrees. The skin of the extremities is a few degrees lower. In one case histamine was released in the skin at 45 degrees and in another at 80. The skin cells could not tolerate a degree of coldness that has no ill effect on normal cells.

FIG. 9

HISTAMINE AND ANAPHYLACTIC SHOCK

According to theory an antigen-antibody reaction results in mutual damage, as a consequence of which a poison, histamine, is released from the cell. This same release can be effected in the absence of an antigen-antibody reaction if one is a victim of physical allergy. In the latter case degrees of heat, cold, sunlight or mechanical irritation which are harmless to most people may so injure the tissues that cells release histamine. Histamine causes capillary blood vessels to relax or dilate and injures the lining membrane to such an extent that fluid which should be held inside the blood vessel leaks through the membrane into the tissues. The loss of so much fluid from the vessels lowers the hydrostatic pressure inside them. In other words, the blood pressure falls. Normal blood pressure ranges from 110 to 145 millimetres of mercury. If it falls far below 110, such as to 60 or 50 millimetres, the positive pressure inside the blood vessels is no longer sufficient to propel the blood through the vessels in the brain. Brain cells cannot function normally without an adequate supply of oxygen in the blood. The victim loses consciousness. Other tissues are affected in a similar way. The resulting condition is called shock.

Histamine also causes the smooth muscles of the bronchi to contract, thus narrowing the air passages so that not as much air can get into or out of the lungs. This produces wheezing, and the condition is termed asthma. The reaction in the bronchi further reduces the amount of oxygen available for the brain cells and other cells. We do not yet know definitely whether the smooth-muscle contraction is due to direct stimulation of the muscle cells by histamine or whether it is indirect, resulting from the reaction of the capillaries.

Histamine is derived from histidine (Fig. 1), an amino acid which is present in all living cells.

Blow Hot, Blow Cold!

The first instance of an abnormal response to cold, of the type that we now call physical allergy, was reported in 1866. From then until 1923 there were occasional descriptions of persons who fainted or had hives or other symptoms from degrees of cold that were harmless to average persons. William Duke, an American, described reactions to sunlight (1923) and to heat and cold (1924) which he believed to be allergic. He coined the expression 'physical allergy.'

One who is mildly reactive to cold may have symptoms during only the first cold days of winter, remaining well later on, even in midwinter when it is much colder. This is because such a person becomes adjusted or acclimatized to the altered temperature. Others react to the actual degree of coldness. They will have no trouble in early winter, their difficulties commencing only when the thermometer is very low. Still others react more to sudden changes in temperature. They may do well in a warm house but have symptoms after going out into the cold. If they remain in the cold they do nicely. They may have trouble in midsummer, with sneezing or wheezing or hives, after entering an air-conditioned building. Those who are allergic to heat have comparable grades of response.

Some curious paradoxes have been seen, of which the following are examples. A lady had throbbing headaches and flushing of the skin after exposures to cold. Ice cream or chilled food made her throat swell. Cold air on the face also caused it to swell. She stayed in a room with a temperature at about 70 degrees and had no symptoms. But when her arm touched a metal cabinet the temperature of which was two degrees higher than that of the room the arm became irritated and swollen. The room did not seem cold but the cabinet did. Metal, being a good conductor, had removed heat from the arm more rapidly than did air. The arm actually was cooled more rapidly than the rest of the body.

Physical and chemical allergy may coexist in the same person. In such a case histamine may be released either by the direct stimulation of heat or cold or as a result of antigen-antibody reaction. A boy with asthma and hives went to a doctor to be tested. The latter, taking his extracts from the refrigerator, tested the boy with a series of little scratches, rubbing in solutions of the suspected foods. Every food reaction was positive. The doctor concluded that the boy's hives had interfered with the test.

That evening as the lad and his mother drove home they stopped at a dairy for a bottle of milk. The cold bottle lay for some time against the boy's leg. When he reached home there was a large hive on the leg.

Upon hearing of this the doctor warmed his extracts to room

temperature after taking them from the refrigerator. The tests then worked satisfactorily, with many negative reactions and a few positives. It thus became evident that the boy was allergic both to foods and to cold.

It has been found that many instances of drowning, presumably caused by cramps, are really allergic shock due to cold. Several persons who have been rescued have later been found allergic to cold.

The person who sunburns much too easily on the beach is not allergic to actinic rays. He is unusually susceptible, either because he has not become hardened by exposure or because he does not have enough protective pigment in the skin. He reacts in a normal manner, the way in which any person would respond to an overdose of sunlight. One who, on the other hand, develops hives or eczema after exposure reacts in an altered or abnormal way. He is allergic to sunlight.

I have mentioned effort as a cause of physical allergy. This is a phase of allergy to heat, the heat being produced internally. A lady suffered near collapse after swimming across a mountain lake. Cold allergy was suspected, but she did not react to cold. On the contrary, she was found strongly allergic to heat. In spite of the cool water she had created enough body heat, from the effort of swimming, to cause severe symptoms.

Mechanical irritation, a cause of physical allergy, is exemplified in those who develop weals wherever they scratch themselves. The condition is termed dermographia or skin writing.

Chapter XI

BLAME IT ON GRANDFATHER

DR. SMITH HAD TOLD CAROLINE'S MOTHER THAT ALLERGY IS HEREDitary. While the inheritance is often obvious, it is sometimes hard to trace. If it were a matter of the transmission of hay fever or sick headache or of asthma through generation after generation, the problem would be simple. But one does not inherit a particular allergic symptom or sensitization to a given allergen such as ragweed, strawberry or tomato. The attribute which is passed through successive generations is the tendency to become sensitized to one thing or another. What that thing will be depends more on environmental exposures. The location of the reactive tissue within the body also depends in great measure upon post-natal factors. As a consequence one member of the family may have asthma due to orris root; another, hay fever caused by elm pollen; a third, indigestion from lobster; and yet another may experience sick

headache after eating chocolate. While the tendency is inherited, the manner of its manifestation is not.

It may be quite difficult to convince a man who has his first attack of eczema at age fifty and finds that it is caused by wheat that his disease is inherited, especially if there is, so far as he can recall, no allergic history in his family. Indeed, it is hard even to convince him that wheat is responsible when he has eaten it all of his life without trouble. This is another of the many features which make allergy such a strange disease.

With our present knowledge we must content ourselves by explaining to this man that when inheritance is heavy, coming from both sides of the family, allergic symptoms are more likely to occur in childhood. When inheritance is unilateral, symptoms may first appear later in life. When there is no apparent inheritance the probability is that the responsible gene, that extremely small part of the cell which controls heredity, has lain dormant through several generations. Here, again, symptoms are not likely to appear until after maturity. Had our man died before his fiftieth birthday he would never have known that he carried this gene, and yet one of his children might have inherited it from him, becoming allergic at some time in life. This child would certainly insist that his father had never been allergic. In other words, the inherited tendency may for one reason or another lie dormant through several generations.

From 50 to 75 per cent of allergic persons have a family history of allergy as contrasted with a similar history in only 7 per cent of non-allergic persons. Nearly three-fourths of all children with bilateral inheritance develop the disease, and most of them do so before age ten. About half of those with inheritance through only one parent will eventually become allergic. One-third of these and one-fifth of those with no recognized inheritance develop symptoms before age ten. The heavier the inheritance the greater will be the proportion of children who become allergic and the greater the number of allergic symptoms in each offspring.

Much remains to be learned. Nearly all investigators agree that there is an hereditary factor. There is not as great agreement as to how it works. Among five important groups of investigators one has concluded that the inheritance is as a Mendelian dominant; the second, as a Mendelian recessive; the third, a partial dominant; and the fourth, a partial recessive. These comprise about all of the more important possibilities. The fifth investigator doubts if inheritance plays an important part. Four out of five, or 80 per cent, believe in inheritance but they do not agree on the mechanism.

Allergy in Twins

Allergy in twins is especially interesting. I have mentioned (page 35) the twin daughters, one of whom had had urticaria

while the other had had no allergic symptoms. When the latter received antitoxin the evidence of sensitization was most regrettably convincing.

Not many allergic identical twins have been studied. In one series of six pairs, three pairs showed identical sensitizations. In a seventh pair both children developed asthma at age four and both reacted to the same allergens—wheat, mustard, radish and ragweed. Presumably they had both been on the same diet. In an eighth pair one had pollen asthma while the other had no evidence of allergy. In two more pairs of twins all had asthma. In the eleventh set both had asthma, due in one case to pollen, in the other to food. Among several pairs of identical twins studied in Cleveland from birth to age eight there were instances in which only one of the two developed active allergy. Of course, the other may become allergic later or may have been allergic without having symptoms.

Sensitizing Exposures, Before and After Birth

One of Richet's two basic conclusions was that the allergen must be harmless on the occasion of the first exposure. It is not until after the sensitizing contact that the cells become allergic.

When egg protein is first injected into a guinea pig nothing happens. After the second injection trouble ensues. How can one become allergic to egg when nobody has ever injected egg into one? Under certain conditions egg protein taken by mouth may be absorbed undigested through the intestines and into the blood just as though it had been injected through the skin. A period of indigestion, some vitamin deficiency favouring abnormal absorption, over-eating, temporary disturbance in the activity of the digestive juices or some other factor might promote absorption of undigested protein. This has been proved by several investigators.

In human allergy it is usually impossible to establish definitely the time at which the first or sensitizing exposure of the body cells took place. But knowledge of what happens in animals justifies assumption that the same occurs in human beings.

Occasionally we find fairly definite evidence of the first exposure. There is a lady, now eighty years old, who has been unable to eat chocolate since her early teens. As a girl she liked it so well that she once ate nearly all of a big box of chocolates. It gave her indigestion, caused by food outrage rather than food allergy. A few weeks later she had some more. This time all was not well. Within a few minutes she was having severe hay fever for the first time in her life. For nearly seventy years she has been unable to eat chocolate without encountering difficulties.

About 10 per cent of those with pollinosis date their trouble from soon after a nose or throat operation performed during the pollen season. One can understand how the sensitizing dose of

pollen might have been absorbed through the raw, unhealed mucous membrane.

An infant eight months old became ill. He coughed and wheezed, and his mother thought he had croup. He had a fever. Fearing pneumonia, the mother called the doctor, who promptly recognized the condition as asthma. She had thought that there was no fever with asthma. The doctor explained that fever may be present, especially in children.

The following morning he made a few tests. The infant reacted to wheat. He had had toasted bread just an hour before his asthma had commenced. "But," argued the mother, "as I understand it there must be a sensitizing exposure. He never had wheat before in his life."

This is not an unusual statement for mothers to make. They are usually mistaken. In this particular instance the child had been teething a month earlier and his mother had let him chew zwieback.

There are, however, authentic instances of children reacting to food eaten for the first time. Chocolate serves as a good example, inasmuch as the mother can know quite definitely when it is added to the diet. Eggs cause trouble on first ingestion more often than any other food.

For a while it looked as though this one fact might prove that human allergy is basically different from anaphylaxis in animals. But when it was shown that the unborn babe may absorb antigenic protein by way of his mother's blood the explanation became obvious. He had received his first or sensitizing dose before birth, when still receiving nourishment from his mother. Children born already sensitized are likely to react to those foods which their mothers have eaten in excess to satisfy the abnormal food craving which often develops during pregnancy.

Chapter XII

SHALL I SNEEZE, WHEEZE, ITCH OR ACHE?

THERE IS ONE MORE PHASE OF THE ALLERGIC REACTION WHICH WE should discuss before passing on to consideration of what to do about it. This is the matter of the shock tissues. Here and there in the foregoing discussion I have remarked on the dissimilarity of the various allergic symptoms. Why does the reaction appear in so many different forms?

The answer is found in the manner of response in different animal species. Let us recall that the two outstanding changes in anaphylactic shock are spasm of smooth muscle and increased

permeability in the smallest blood vessels, the capillaries, so that serum oozes out into the tissues. Although tissues in various parts of the body respond in the guinea pig, the outstanding change is spasm of the muscles in the air passages, or bronchi, producing a condition similar to human asthma. The spastic bronchi act much like ball valves, so that air leaves less easily than it enters. As a consequence the lungs are widely distended, too full of air. There are also symptoms of irritation in the nose. Death in the anaphylactic guinea pig is predominantly due to failure of the respiration. The rabbit shows a different picture. The muscles in its bronchi are not contracted enough to cause asthma, but those in the blood vessels of the lungs are in severe spasm. Symptoms are associated with this disturbance in the circulation, and death is due in part at least to heart failure. In the dog, shock is accompanied by pronounced fall in blood pressure with extreme congestion of the liver and increased permeability of the capillaries. The horse and cow have predominantly intestinal symptoms, including diarrhœa. Urticaria occurs in the horse, cow and monkey. Increased capillary permeability with consequent swelling of the tissues occurs in most animals.

Smooth muscle is better developed in the bronchi of the normal guinea pig than in these other animals, while vessels of the rabbit's lung and those connected with the dog's liver show similar preponderances. The reaction is stronger in those tissues where there happens to be unusually well-developed muscle. This varies with the different species of animals. We speak of these special areas as shock organs or shock tissues.

Some persons react like guinea pigs, others like dogs, some like horses, and some of us behave like monkeys. An allergic person may react like several of the animals, his bronchial shock tissue being responsive at one time, his intestinal tract at another. At times a single allergen will cause reactions in more than one shock tissue. In other cases different allergens will always stimulate just one tissue.

A man may have sick headaches regularly after eating carrots. He may also be allergic to potato, responding with hives. Carrots never cause his hives nor do potatoes produce headache. Each shock tissue is reactive to its own allergen and will not respond to the other. This is not true in all cases. Another man is allergic to mushrooms. They give him hives at one time, headache at another, and on still other occasions they produce diarrhœa, with or without hives or headache. Sometimes they just cause toxic fatigue, making him tired, achy and irritable.

If the allergic response is extremely severe, so many of the capillaries will become permeable that much fluid will leak out of the blood vessels into the tissues. The blood pressure falls until insufficient blood can be circulated to the brain and other tissues.

The victim loses consciousness and, if the condition persists, passes into shock (see Fig. 9).

The symptom of the moment will depend in great measure upon which shock tissue happens to be reactive at the time. It also depends in part upon where the allergenic excitant comes in contact with the body cells.

Inhaled allergens are more likely to stimulate the shock organs in the nose or bronchi, those which are eaten are more likely to cause digestive disturbances, while those which come in contact with the skin may affect it predominantly. Those which have been introduced directly into the body with a hypodermic needle or which have penetrated into the blood from the alimentary tract may stimulate any or all of the shock tissues.

In Summary

What we know of allergy was not discovered in a day. It represents tireless investigation by hundreds of scientists for over thirty years. It was inaugurated with the discovery that a dog does curious things after receiving injections of material from a sea animal. Interest, at first academic, became more general when it became apparent that this newly acquired knowledge could be applied to the study and treatment of certain diseases.

Attempts at treatment were begun early, long before we had learned as much as has been herein summarized. Early efforts were not always successful, but each series of experiments enabled us to learn more of allergy. Much of the knowledge which we have discussed has been gained through study of patients' responses to treatment.

The application for treatment of knowledge gained in the laboratory must of necessity come slowly. It is said that the great Richet himself had an idiosyncrasy to egg. And yet several years passed after his work on Neptune before it occurred to him that his own malady might be explained on the basis of his momentous discovery.

We shall now turn back the pages of time to learn what the doctors were doing toward applying the discoveries of anaphylaxis for the betterment of mankind.

PART THREE

NEXT CAME TREATMENT

Chapter XIII

ON ALTERING AN ALTERED TENDENCY

THE SUMMER OF 1913 WAS PLEASANT AS SUMMERS GO, BUT NOT FOR one lady whom we shall call Madame X. For several years no summers, or other seasons for that matter, had been pleasant, for she was a victim of indigestion. Madame X had consulted many doctors, who had talked of ulcer or gall bladder and appendix, but none had been sufficiently convinced of the correctness of his diagnosis to insist on an operation. At last she consulted a young doctor not long out of school. He had been reading much of this phenomenon called anaphylaxis and had heard of Dr. Schloss's success in curing a young boy's allergy to egg.

After careful study of Madame X's symptoms and a very thorough examination he watched her from day to day until he was at last sure that her difficulty was due to an idiosyncrasy to chicken. Had he told her that she had an idiosyncrasy she might have listened, but when he spoke of anaphylaxis she became suspicious. This young doctor with his new-fangled ideas was just experimenting. Besides, she liked chicken. She had it in her food in one form or another at least twice each week. She protested, "Treat me and get me well, but don't take my chicken from me." And she continued to eat it.

The doctor saw but one solution—to call in an older man who had the newer ideas and could speak with such authority that Madame X would listen. So he called Victor Vaughan.

After the consultation Dr. Vaughan called for a bowl of chicken soup and a fountain syringe. I suspect this was the first time in history that a human being received an enema of chicken soup. She had one each day for several days, during which her symptoms gradually improved. When the doctor announced that she could have chicken whenever she wished, provided she would take a chicken-soup enema beforehand, she probably concluded that the world had gone mad. But it worked. The only difficulty was the distasteful preliminary preparation for the pleasure of a slice of

chicken. Concluding that the game was not worth the candle, Madame X finally renounced her favourite food. It was a roundabout way, but the doctor had achieved his purpose and the patient had lost her indigestion.

Most of us know that the days of miracles have passed. After the parlour magician has done his trick we raise our eyebrows and remark, "Now tell us the secret." What was the secret with Madame X?

Dr. Vaughan was a scientist, more interested in test tubes and guinea pigs than in aches and pains. In his study of protein split products he had confirmed Rosenau's and Besredka's claims that they could counteract the anaphylactic state. Repeating one of Besredka's experiments, with Madame X as the guinea pig, he had produced a condition known as antianaphylaxis.

Antianaphylaxis or Desensitization

If man can so change the physiology of an animal with one or two injections of a foreign protein that he will react in an altered manner, might not there be some way to reverse the process—to so change an altered animal that he will react in a normal way? Several early investigators proved that to a limited extent this could be done. Milton Rosenau and his associate, Dr. Anderson, made most important contributions. Otto in Berlin and Richet in Paris did likewise. Besredka gave the procedure a name. He called it antianaphylaxis. We speak of it to-day as desensitization or hyposensitization.

If a guinea pig be sensitized to egg white or some other protein, a second injection after ten days will be fatal, provided sufficient antigen is given. Guinea pigs have been sensitized by one-millionth of a cubic centimetre of horse serum. This would be about one-fifty-thousandth of a drop. Not much more is needed to produce shock on second injection. One drop would be enough, especially when injected directly into the blood.

If one were to sensitize fifty or a hundred guinea pigs with the same dose of serum and attempt to produce anaphylactic shock after the proper interval, one would find that there is a minimal lethal dose. This means that there is a dose, possibly somewhere around one drop, which will regularly cause death. Larger doses would kill but smaller doses usually would not. In the latter case animals would become ill but would recover. That smallest dose which kills regularly is the minimum lethal dose, or M.L.D.

Now let us inject a quantity slightly below the M.L.D. into a sensitized pig. The animal will become ill but will recover. After two or three days let us inject him again, this time giving somewhat more than the M.L.D. Will the pig die? If not, what will happen? As a matter of fact, nothing happens. The animal remains quite well and happy. Apparently the allergic state has been cor-

rected. In terms of the side-chain theory, the antibodies have been used up. If there are no more antibodies available to combine with serum antigen when it is re-injected a few days later, there will be no reaction. Possibly so many of the sessile or attached antibodies (which as you recall are the ones that combine, in allergy, with the antigen), have been combined or neutralized that there are not enough left uncombined to cause difficulties on the next injection. This was an early explanation.

The change unfortunately is not permanent. After a time additional specific antibodies are produced, and within a few weeks antianaphylaxis or desensitization has disappeared, the animal being again sensitized.

How can one prevent this return of sensitization? If one were to continue with injections of the antigen while the animal is still antianaphylactic, giving them every few days, one might keep antibodies persistently used up. Rosenau and others did this. They treated antianaphylactic animals at regular intervals. No unusual symptoms resulted. As long as injections were continued the animals remained desensitized.

Besredka found this could be accomplished by introducing the antigen into the rectum as well as by hypodermic injection. Slow absorption through the mucous membrane of the lower intestinal tract at first made the sensitized animal ill, but with repeated treatments the antianaphylactic state was induced and maintained. This was what happened to Madame X.

Its Application to Inhalant Allergy

Wouldn't it be splendid if some method based on this principle could be applied in the treatment of allergic persons? Leonard Noon and John Freeman of London thought so. They believed in Charles Blackley's theory that pollens cause hay fever. They knew that the germ theory had been disproved. They knew that Dunbar's treatment based on his toxin theory had failed. They also knew that pollinosis is an idiosyncrasy because it affects some people but not all, and that the symptoms, nasal irritation and bronchial spasm, were identical with those of anaphylactic guinea pigs. Why couldn't pollinosis be an allergic disease? If it is, why couldn't one give injections of pollen extract to produce the antianaphylactic state? It was worth trying.

Of course there were difficulties to be ironed out, such as the proper dose, the proper interval between injections and the proper time before the pollen season at which to start treatment. The greatest problem was that one cannot treat human beings like guinea pigs. It may be all right to give a guinea pig a dose that will make him frightfully sick, almost kill him. But one cannot do this to one's patients and expect to continue having patients. Fortunately the laboratory investigators had provided an alternative.

They had found that if instead of giving a single large non-fatal shocking dose one were to give very small doses, frequently repeated and of increasing size, the antianaphylactic state would be produced without the animal having been made obviously ill.

So this was what Drs. Noon and Freeman did. They collected a group of patients who for many years had endured the discomfort of hay fever and asthma in the springtime. They recalled that Blackley had put a little grass pollen in the eyes of such patients. Conjunctivitis of short duration had resulted. Rubbing the pollen into a scratch would produce a small hive. Neither reaction occurs in normal persons. This was helpful because here were two methods for determining that the right type of person was being treated.

The patients were willing enough to try anything which would give them relief from their regularly recurring discomfort. They knew too well the truth of the old adage that no occurrence in the future is certain save death, taxes and hay fever.

The doctors took no chances. Their first doses were extremely small—the extract of one millionth of a gram of pollen. This would be about one four-millionth of a teaspoonful. It would correspond to about one five-millionth of a lump of sugar. Two or three months before the season the patients started taking their injections once a week or oftener. The injections were occasionally followed by slight discomfort, a short period of hives or a very mild attack of hay fever, but they had confidence in these doctors and let them gradually increase the dose until at the onset of the hay-fever season they were receiving two or three thousand times as much as at the beginning.

Imagine the doctors' anxiety when the fateful day arrived. And imagine their thrill of exultation when well into and on through the season their patients returned each week, as jubilant as they, reporting a degree of relief which they had never before experienced.

Here was something worth telling the medical world about, which Noon and Freeman did in 1911. Other doctors tried it. They found that it worked. To-day protective desensitization for pollinosis is used the world over. There have been many improvements and variations from the original programme of Noon and Freeman, but the same principle applies in all.

Not all patients are relieved to the same degree. If in each case we could produce non-fatal anaphylactic shock with consequent antianaphylaxis just before the season, the results might possibly be excellent in all cases. But here we have a dilemma. In curing one disease we must not make our patient equally ill from another, even though it be of short duration. We must take the middle ground, giving such doses as have been proven safe, even though larger ones might be more effective. For this reason we customarily evaluate relief after treatment, not as total cure but in terms of

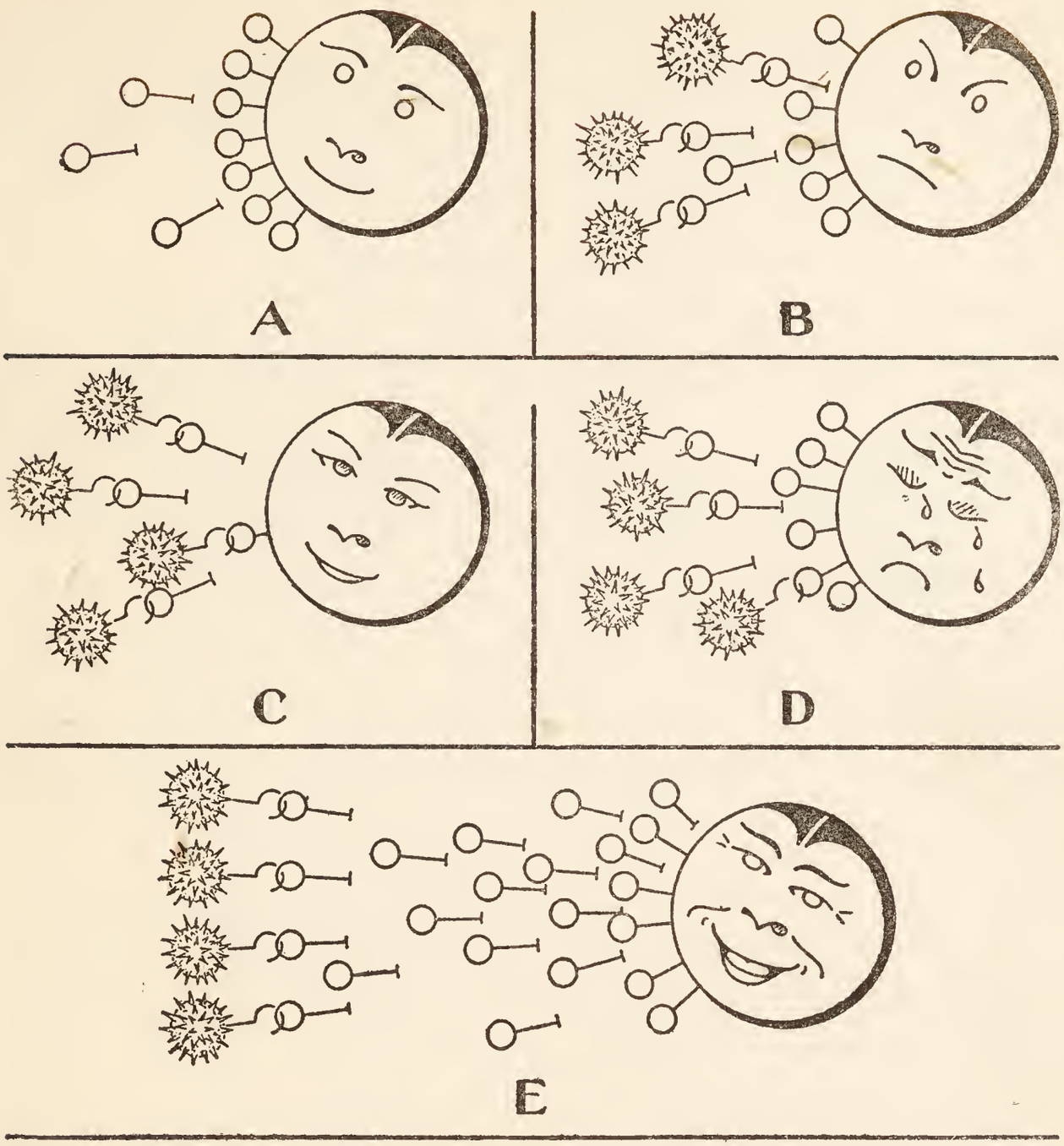

FIG. 10

TWO WAYS IN WHICH DESENSITIZATION AGAINST POLLEN OR OTHER ALLERGEN MIGHT BE ACCOMPLISHED

In A there are a few floating antibodies with many attached. This is poor protection. The first injection is so small that much of the antigen is neutralized by the few floating antibodies (B). Some reaches the attached antibodies. When attached antibody combines with foreign protein the injured cell sheds it.

Successive doses are larger. More antibodies are shed until (C) all have become detached from the cell. They have been used up. When the pollen season starts there are no more antibodies to combine with pollen protein. Consequently, the cell is not disturbed.

However, tests prove that free antibodies are still present in desensitized blood. It seems more probable that the sequence represented in D and E is what happens.

In D, as in B, the floating antibodies are neutralized and a vew few attached ones are injured. These are released from the cell, which manufactures more to take their place (D). It produces so many that more are shed, greatly increasing the floating antibodies (E). The cells put out a barrage of floating antibodies. There are still attached ones, but these are protected by the defence barrage. If this is the true mechanism, we may use the term immunization as logically as desensitization both implying the same process.

percentage or degree of relief as compared with seasons when the patient did not receive treatment.

You now know why treatment must be taken each year and why one course of treatment will not give permanent relief. Anti-anaphylaxis is a temporary state. If injections of the allergen are stopped, sensitization gradually returns.

Its Application to Food Allergy

Things were happening on the other side of the Atlantic. A child was brought for treatment to Dr. Oscar Schloss, a New York pediatrist. There was a most unusual story of idiosyncrasy. The lad had had diarrhœa when ten days old and was treated with barley water and raw egg white. This relieved the complaint and caused no unpleasant symptoms. He received no more egg until he was fourteen months old. Almost immediately after eating part of a soft-boiled egg he cried out, clawed at his mouth, and his tongue and mouth swelled until they were many times normal size. Hives soon appeared around the mouth. He recovered reasonably soon and refused thereafter to eat eggs. You who now know the mechanism of allergy will recognize the initial or sensitizing dose taken during a period of digestive upset when egg protein might be absorbed into the blood and the second or shocking dose many months later.

When the boy was two years old his mother noticed that if he were to play with empty eggshells he would break out with hives on his hands and arms. At about this same time he ate eggs for a third time. He vomited. The lips, tongue and face again swelled, and he developed hives over his whole body.

He had three repetitions of this experience : once when egg was given experimentally, concealed between slices of bread, once when he ate cake containing egg, and again after eating a small portion of a roll, the top of which had been glazed with egg white.

Schloss suggested that the boy's experiences might be due to this new condition, recently receiving so much attention, called allergy. But, a true scientist, he searched for some means of proving the relationship.

Milton Rosenau had drawn blood from a sensitized guinea pig, injected it into a normal non-sensitized animal and found that the second animal was now as allergic as the first. Antibodies had been transferred in the blood and had become fixed in the new animal's cells. The first animal was actively sensitized, the second passively so. There was this difference : the condition was not permanent. Passive sensitization disappeared after a month or six weeks. The cells had absorbed the antibodies produced by the first animal's cells but they had not themselves learned to manufacture antibodies. Animal No. 2 remained sensitized only until the receptors from animal No. 1 had deteriorated.

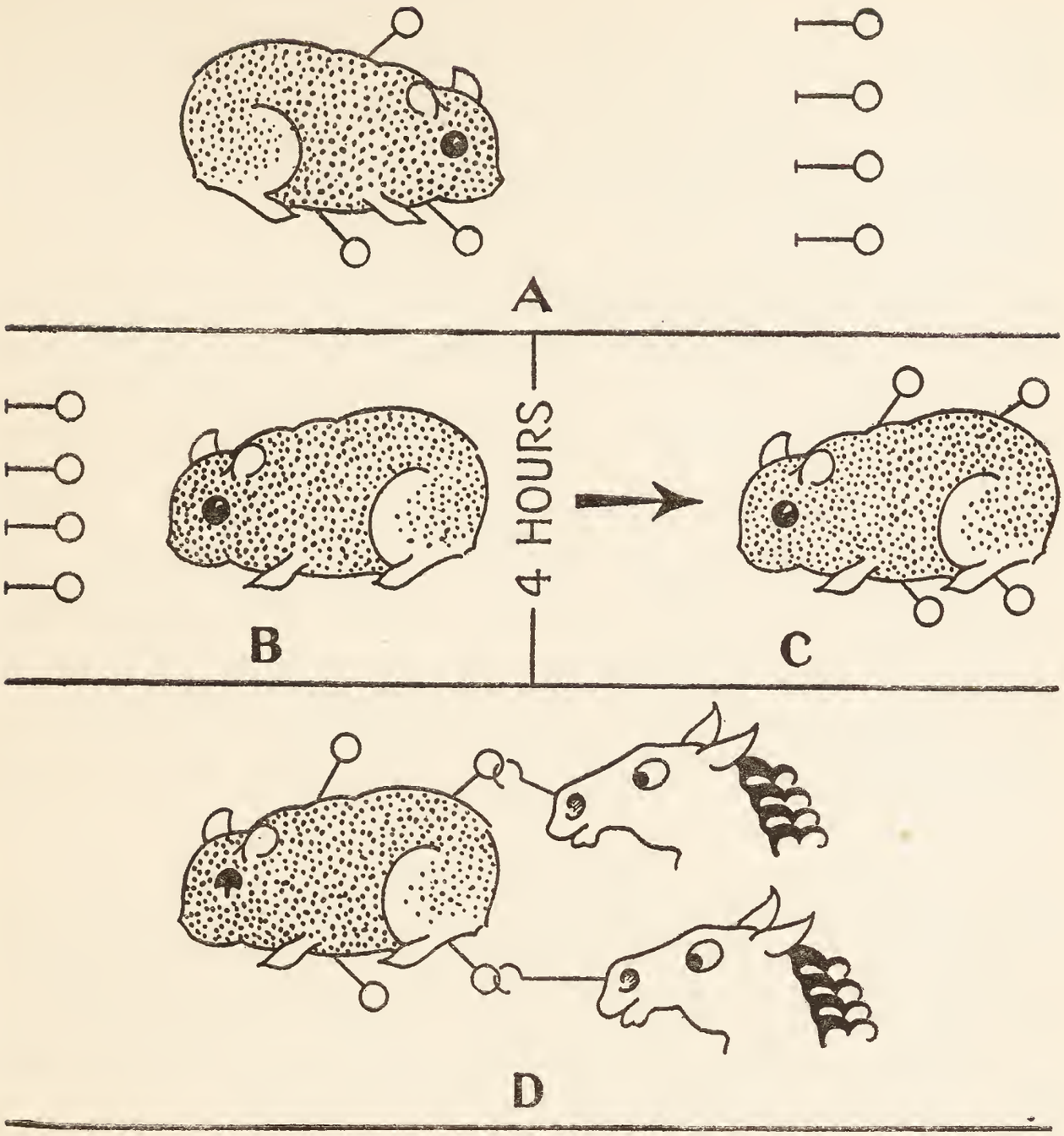

FIG. 11

PASSIVE TRANSFER OF SENSITIZATION

A guinea pig has been sensitized with horse serum (A). Its cell has horse antibody attached (left). It has shed some antibodies which are floating (right). Let us inject pig A's blood into a normal guinea pig (B). Floating antibodies now circulate in this pig's blood. As they pass along they gradually become attached to guinea-pig cells (C). After a few hours the second pig is sensitized to horse serum.

If horse serum is injected into pig A, this animal will have anaphylactic shock provided so much serum has been given that the floating antibodies do not neutralize all of it and some reaches the attached antibodies. Pig A is actively sensitized to serum.

Pig C is passively sensitized. The cells have gone through no active process of manufacturing antibodies. They have received them as a gift from pig A. This state is termed passive sensitization. If horse serum is now injected into pig C, he will have anaphylactic shock (D) just like pig A.

Active sensitization of pig A is fairly permanent. Passive sensitization (C) is not permanent. The antibodies are loosely attached to the cell. After a month they have disappeared, and a second injection of horse serum then causes no trouble.

In 1909 a German physician, Dr. Bruck, injected the blood of a man who was allergic to pork into a guinea pig. He next injected pork protein into the animal. The animal went into anaphylactic shock. Here was a method, the method of passive sensitization, by which Schloss might show that the lad's egg idiosyncrasy is truly anaphylactic. He injected the boy's blood into a guinea pig. Later he injected egg white. The animal had typical shock.

So far Schloss had but repeated and confirmed Bruck's experiment. Now, like Noon and Freeman, he wondered whether the principles of antianaphylaxis might cure the boy of his idiosyncrasy.

He mixed the white of a raw egg with water and diluted it so many times that you would scarcely have thought there was any egg left. He fed this to the boy with a medicine dropper. Nothing happened. He kept on giving this curious medicine every day, increasing the number of drops each time and gradually increasing the strength of the solution. Here again was desensitization, but desensitization by mouth rather than with a hypodermic syringe. He finally increased the tolerance to such an extent that the lad could eat eggs in moderation with no consequent discomfort.

Here again was something well worth telling to the world. Schloss published his report in 1912.

To-day's Methods

Bruck and Schloss had proven that human allergy and experimental anaphylaxis depend upon an identical reactive mechanism. Noon, Freeman and Schloss had shown the way to a new treatment which held promise of relief for those hundreds of thousands who had had to go through life acknowledging that they had an idiosyncrasy and that nothing could be done about it.

Two methods of desensitization were now available—hypodermic and oral. We use both to-day, although oral desensitization to foods is not as regularly successful as hypodermic desensitization against inhalant allergens. Since there are many kinds of meats, fruits, vegetables, etc., and substitute foods are usually at hand, avoidance of offending foods is preferred, as a rule, to desensitization.

Avoidance has an advantage over desensitization. Evidence suggests that if cells sensitized to an allergen are not regularly stimulated to produce antibodies, by repeated exposure to the allergen, they gradually lose their sensitization. If I am constantly rowing a boat I grow protective callouses on my palms. If I handle no oars for many months the thickening of the skin disappears. For true cure, therefore, avoidance seems preferable to desensitization. We have seen that antianaphylaxis is not curative and that the allergic state recurs. The difficulty with some allergens is that four or five years of avoidance may be necessary before sensitization is completely lost. The hay-fever victim, exposed every year, cannot

avoid the allergen long enough to lose his sensitization. He must therefore be hyposensitized.

Although we customarily speak of the procedure as desensitization, hyposensitization is a better term, for one is not completely desensitized. What we do is diminish the degree of sensitization. We lessen it. We undersensitize. We hyposensitize.

Desensitization usually lasts for several weeks. Since the average pollen season is of six weeks' duration or less, pre-seasonal treatment usually protects, and it may be unnecessary to give further treatment during the season. Other methods of desensitization, especially the co-seasonal and the perennial, are modifications based upon the same general principle.

Chapter XIV

ON TRANSFERRING A NON-CONTAGIOUS DISEASE

AS THE DOCTOR WAS STARTING HIS TESTS THE NEW PATIENT INQUIRED how many scratches would be made. The doctor told him. He appeared not altogether pleased and before long gave voice to his doubts : "The last time Doctor Blank did twice that many."

This is reminiscent of the early days of X-ray diagnosis when the patients too often believed that "if the X-rays were put on them," the resulting information would be infallible, irrespective of the intelligence of the man whose duty it was to interpret what he saw. To-day the same holds true in allergy. "Two hundred tests are bound to be twice as good as one hundred." To some persons a half-dozen scratches on the arm at any time in the preceding ten years imply adequate skin testing. Allergists of experience realize that improvements are being made so rapidly that if they themselves made the tests four or five years previously, and if the patient did not improve satisfactorily, the study should be repeated, using the newer technique.

Routine Skin Tests

In nearly all cases sufficiently allergic to require consultation with a doctor, sensitization is multiple. The patient reacts to several allergens, not to just one. Doctors have learned from experience what substances are likely to cause sensitization and have found that it is well to have a standard test series of possible offenders. The patient is tested with these irrespective of whether they are under suspicion at the moment. Unsuspected allergens are often discovered in this way. Thus a person who complains only of hay fever during the ragweed season might be tested just with ragweed extract. But we know that other pollens in the air at the same time, such as golden-rod, cocklebur and fall-blooming elm, may

complicate the situation. It is as important to know that these other pollens are negative as that ragweed is positive. Even though the symptom may be seasonal hay fever and the story does not suggest food sensitization, such patients often give positive food reactions. When this happens dietary restrictions during the season may improve the results. This may be true even though the patient has not been conscious of trouble from the 'positive' foods.

It is never necessary to test with all known allergens. A French physician once tabulated all of the foods that go into the average Frenchman's menu during the four seasons. His list contained four hundred different items. About one hundred food tests usually suffice for routine study, with the proviso that additional tests may be needed for other special foods under suspicion in the individual case.

The doctor should use discretion in the selection of his routine test materials. A friend once told me of a lady past middle age being tested with mother's milk !

Skin tests are not infallible. Some remain negative when they should have become positive. Others are positive even though study proves later that the substance is not harmful. Taken as a whole, skin tests give invaluable information and do so very quickly. Without them the same knowledge might be gained, but only after weeks or months of study.

The History of Skin Testing

Skin testing was employed in the study of allergy for some time before doctors realized that it might be used for diagnosis. The earliest test of which we have record is said to have been made in 1835 by a Dr. Kirkman. Having hay fever, he tested grass pollen by sniffing it and rubbing it on his hand. Blackley tested himself by rubbing small amounts of pollen on to scratches, by sniffing it to see whether he would sneeze and by putting small quantities on the eye. Just who first thought of the method and how he happened to do so will probably remain unknown.

In any event, the man who first did a skin test by the scratch method probably made his discovery by accident. This is illustrated in Hyde Salter's experiences (1850). When his cat rubbed along his leg he developed hives at the point of contact. If the cat happened to scratch him, the eruption around the scratch was much larger.

It is rather surprising that we have found no early description of an accidental positive skin reaction from the scratch of rose thorns. The probable explanation is, first, that rose sensitization is not common, and second, that a double accident would be necessary, first the scratch and then the implantation of rose pollen in the scratch.

In 1907 the same Pirquet who had coined the term allergy

reported that persons infected with tuberculosis react to a scratch test made with tuberculin. This is an extract made from cultures of the tubercle bacillus. Two years later Dr. H. L. Smith, an American, scratch-tested a man who was known to be allergic to buckwheat. The test with buckwheat flour was positive while a control test with wheat flour remained negative.

During these early years both the scratch test and the intracutaneous or needle test, which came into use shortly after Smith's study, were used as interesting laboratory confirmation of proven sensitization. A man knows he has an idiosyncrasy to egg. It would be nice to prove by some objective method that this is due to allergy. Subjective symptoms are those which the patient feels but no one else can see, while objective symptoms are such as can be looked at and studied. The advantage of the skin test is that it is an objective method. One might take blood from our man with egg idiosyncrasy and, injecting it into a guinea pig, produce passive sensitization as Schloss did with his egg-sensitized boy. But the skin test is simpler, and if it is specific, if it truly indicates sensitization, it is much easier to do.

The early years were spent in establishing the fact that the skin test is specific. It is positive when the food or other allergen is causing trouble. Tests made at the same time with other foods which have not been under suspicion remain negative. In other words, at the beginning it was primarily a confirmative test, for use in cases with idiosyncrasies whose causes were already known.

The specificity of the procedure having been established, it was a simple matter to reverse the procedure. Now let us perform skin tests on persons who have allergic symptoms of unknown causation. We will test with several potential provocative agents. If one reacts and the others remain negative, inductive reasoning points to the positive reactor as the offender. This procedure was first used in 1911 by Robert Cooke of New York.

To-day objective diagnostic tests in allergy include not only scratch and needle tests made on the skin but also eye tests, nasal-contact tests (sniffing the suspected substance, with study of the resulting reaction in the nasal mucous membranes), patch tests and, in some cases, study of changes in the blood, especially in the white cells and platelets. There are special tests for physical allergy. Although these objective methods are of great value, subjective experiences may be equally helpful, and the doctor can ill afford to ignore his patient's discussion of his own experiences and suspicions.

Passive Transfer of Sensitization

One occasionally discovers a real problem in skin testing. An eczematous child has such widespread trouble that there isn't enough normal skin for the tests. Or the skin may be non-specifically reactive, may react to scratches even if no allergen is applied, as

happens in urticaria. Parents may believe that their child is too young, or a young boy may be so spoiled that it would take four nurses to hold him while the tests are being made. Very rarely a patient who should be tested cannot get to the doctor's office.

Thanks to Matthew Walzer of New York these problems are not insurmountable. Two of Dunbar's associates, Drs. Prausnitz and Küstner, found that human beings as well as guinea pigs could be passively sensitized (see Fig. 11). Walzer queried, "Why can't we convert this into a method for identifying unknown allergens, just as was done with the original skin tests?"

He drew blood from the patient's vein, separated the serum in a centrifuge and injected the serum into the skin of a non-allergic person. He injected only a very small amount at several different points. The recipient became passively sensitized in the small zones of skin surrounding the points of injection, areas not more than an inch in diameter. Such passive sensitization lasts for three or four weeks. During this time testing may be carried out on the recipient. The reactions tell us what substances are causing the original patient's allergy.

A young lady had asthma in Puerto Rico but not in the United States. She suspected the *flamboyant*, a beautiful flowering vine which very nearly covered her island home. We could not test her because there was no flamboyant pollen available in the United States. The problem was easily solved. We took a sample of her blood and put it in cold storage. We told her to have someone collect the flowers in Puerto Rico and send them to us by air mail. Upon their arrival we would passively sensitize a small bit of the skin of a non-allergic person with her serum. We would then do the test in Richmond, even though she was far away in the Caribbean.

Allergic Reactions During Transfusions

Normal guinea pigs may be passively sensitized by the injection of sensitized blood directly into the circulation. In man the diagnostic passive-transfer test involves only a small area of skin. Would it be possible to make man allergic in all his tissues? This has been unintentionally done during transfusions. Here the quantity of blood transferred and the method of its introduction more nearly duplicate the animal experiments.

There are two ways by which transfusion might produce allergic symptoms. If the person receiving blood is allergic to some substance which happens to be in the blood of the donor, there may be trouble. The transferred antigen combines with the recipient's antibody.

The sequence may be reversed. Antibodies in the transferred blood may combine with an antigen which happens to be in the body of the recipient. Here are three examples.

A blood donor was sensitized to horse dander. Horse antibody

was therefore transferred into an anæmic patient, the recipient. Nothing unusual happened during the transfusion, and the recipient's anæmia was so improved that one sunny afternoon he went for a ride. All would have been well if he had gone in an automobile, but he went in a carriage drawn by two beautiful horses. He realized very soon that something was happening inside him, producing alarming symptoms which he had never before experienced. For the first time in his life he had an attack of asthma. During the next four or five weeks he had to avoid horses. Gradually the passively transferred antibodies disappeared, until he could ride once again in comfort.

Another donor had horse asthma. This time the recipient's exposure to horse protein was quite different. He had been bleeding and had received injections of horse serum to stop the hæmorrhage. This failing, he was given blood from the horse-sensitized donor. Fortunately the quantity was small and it was not introduced directly into the vein. About an ounce was injected into the muscles. Within a few moments the recipient was wheezing with asthma and scratching a crop of hives which covered most of his body.

In yet another instance a woman who had had a transfusion developed urticaria each time she ate strawberries. To her this was a completely new experience. A month or two later she found that she could again eat strawberries without discomfort. The donor had for years had urticaria from that fruit.

There are examples of the reverse situation : antigen in the donor's blood combining with antibodies which happen to be present in the recipient.

A woman with anæmia was allergic to milk. Her donor, fearing possible depletion from giving away so much of his blood, drank a quart of milk just before the transfusion. The patient had anaphylactic shock soon after receiving the blood in her vein. Fortunately she recovered from this unanticipated catastrophe. There have been similar episodes caused by allergy to other foods : egg, tomato and cabbage.

In another case the donor was a big strapping fellow with plenty of blood. He wasn't worried about depletion and had drunk no milk before giving his blood. Several days previously there had been a little accident which seemed scarcely worth mentioning. He had stepped on a rusty nail and his doctor had given him antitetanus serum, which of course is horse serum. Unfortunately the transfused patient was allergic to horse serum.

You may quite properly raise a question at this point. It is easy to understand in this last case how the foreign antigen, horse serum, came to be added to the donor's blood and carried over into the recipient's body during the transfusion. The matter of drinking the milk seems to be a bit different. Physiologists teach us that protein food taken in the normal way is broken up into its amino

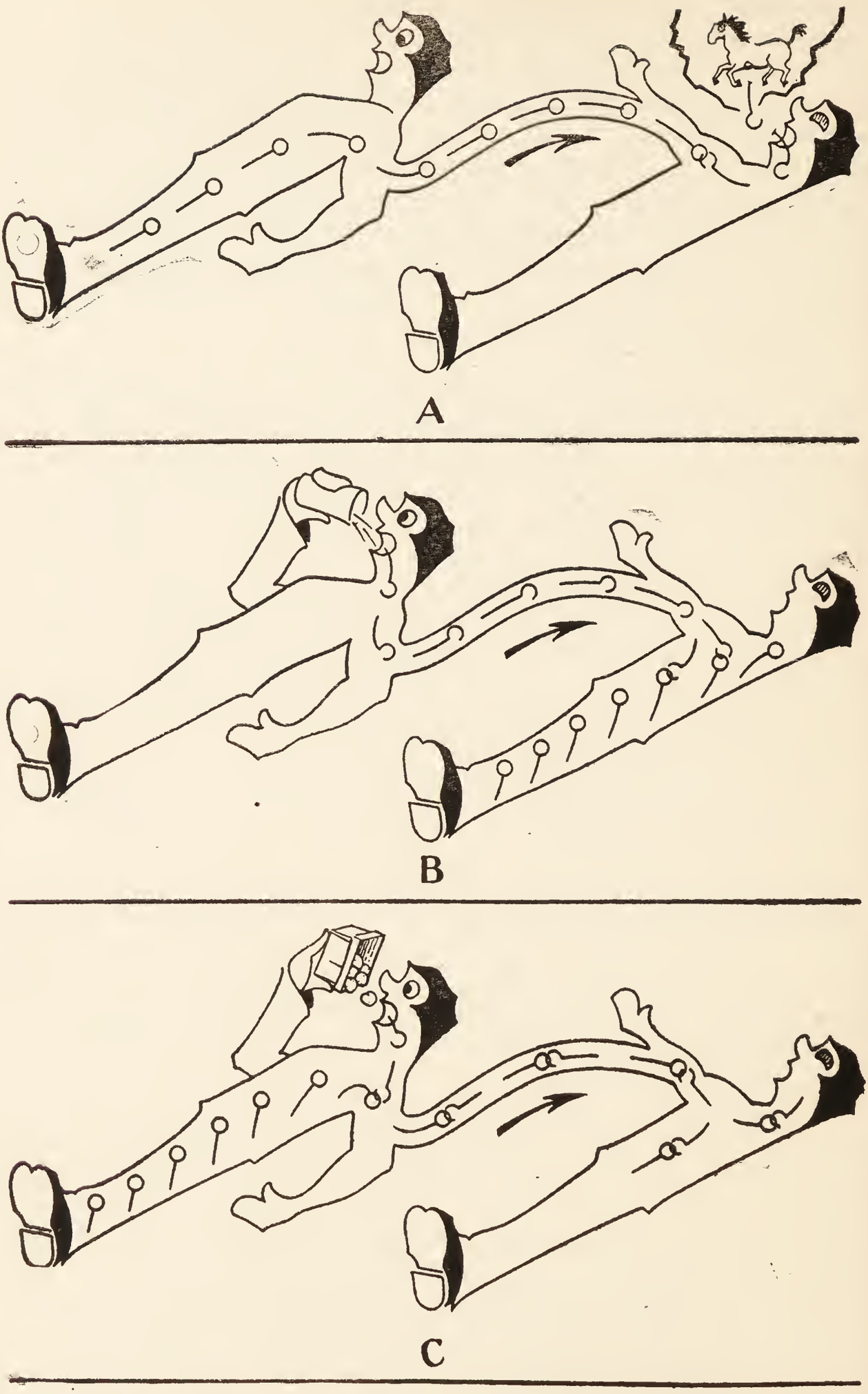

FIG. 12

HOW THE TRANSFUSION OF HUMAN BLOOD MAY PRODUCE ALLERGIC REACTIONS IN THE RECIPIENT

acids before absorption into the blood and that this is what protects the body cells against sensitization. In the milk case the donor was not allergic, and yet milk allergen seemed to be present in his blood in sufficient quantities to be dangerous for the recipient. The answer to this question is not yet altogether clear. We can only say that recent investigations indicate that even in normal digestion a certain amount of incompletely digested protein passes through the intestinal wall into the blood. It is probably partially digested, but it still behaves like protein. It has been digested to that stage where it cannot cause sensitization and is therefore harmless to our donor, but it is still sufficiently like the original undigested protein to cause symptoms in one who is already sensitized to the whole protein.

There is yet a third way in which transfusion may cause allergic symptoms in the recipient. The recipient may have neither antigen nor antibody within him, both of these being transferred to him by the donor. One such case has been reported. The recipient was not allergic. The donor had eaten strawberries, to which he was allergic, shortly before giving his blood. During the transfusion he was having hives, brought on by the recent meal. In all probability his blood now contained histamine. Promptly after transfusion the recipient also broke out with hives. Both had a not too pleasant time scratching. Several weeks later the same donor gave

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FIG. 12

HOW THE TRANSFUSION OF HUMAN BLOOD MAY PRODUCE ALLERGIC REACTIONS IN THE RECIPIENT

Top panel : The donor (left) is actively sensitized to horse dander. He has attached antibodies and some floating antibodies. The latter are transferred to the recipient (right). The recipient is now passively sensitized like guinea pig C in Fig. 11. When later he goes for a horseback ride, inhaling horse dander, the antigen combines with the antibody, causing allergic reaction. This passive sensitization is not permanent.

Middle panel : The recipient (right) is sensitized to milk. Donor drinks a glass of milk just before transfusion. As a result milk antigen is transferred in the blood to the recipient. Antigen-antibody reaction occurs in the recipient, thereby causing allergic symptoms.

Lower panel : The donor is allergic, the recipient is not. Donor's blood contains antibodies for strawberry or some other food. The donor eats this food just before transfusion. At the time of transfusion he is having an allergic reaction such as hives. The recipient also develops hives after transfusion. This might be due to transfer of both antigen and antibody into the recipient, although one would expect them to be already attached and therefore neutralized. A more probable explanation would be that the antigen-antibody reaction in the donor releases enough histamine (see Fig. 9) into the blood so that histamine carried over into the recipient produces allergic symptoms.

The indirect method of skin testing by passive transfer (page 84) is made possible by a mechanism similar to that in the top panel. Only a small amount of the sensitized individual's blood (left) is injected into a spot in the passive-transfer recipient's skin (right). The skin is temporarily passively sensitized. In this type of skin test the recipient does not inhale or eat the test substance but it is injected with a syringe into the same spot of the skin that has been passively sensitized. Four hours, or preferably longer, must elapse between passive sensitization and the skin test, to allow the antibodies to become attached in the recipient's tissues (comparable to C in Fig. 11).

more blood to the same patient. This time he had not eaten strawberries, and had no hives. Only the antibody was transferred. Since there was no antigen the recipient had no trouble.

Allergic transfusion reactions of this sort are rare. Scarcely a dozen have been reported in the entire medical literature. They will probably become even less common, except in emergencies, since they can be prevented by (1) inquiring concerning allergic experiences in both donor and recipient, (2) having the donor avoid eating shortly before transfusion, and (3) by preliminary tests with small amounts of the blood, to make sure that no unexpected reactions will develop.

PART FOUR

ALLERGENS

Chapter XV

FORBIDDEN FRUIT

SENSITIZATION TO FOODS IS THE COMMONEST FORM OF HUMAN ALLERGY. One may become sensitized to any food. It is unusual to be allergic to but one food. In most cases sensitization is multiple. If one reacts to staple foods, such as wheat, egg, milk, coffee or beef, symptoms are apt to be fairly constant and the victim is not likely to discover the cause of his disability, except by skin testing. Those so fortunate as to be sensitized to foods which they eat only occasionally stand a better chance of recognizing a cause-and-effect relationship between these foods and their symptoms and are better able to cure themselves without a doctor's help.

Spontaneous loss of sensitization occurs now and then even though one continues to eat the offending foods, but this is not the rule. Relief is more rapid if the allergen is avoided. We occasionally find persons who are allergic to such a large number of foods that they cannot avoid them all without seriously impairing nutrition. This type of person is likely to continue with trouble in spite of treatment. The following letter illustrates multiple sensitization, with several shock tissues responding.

I have had a world of trouble with two children—one feather sensitive, and it was not discovered until she was sixteen. The other is a food case, an extremely irritable and nervous child as well as very backward. Now he is greatly improved with care as to his food. I do the best I can by observation, as Tommy didn't skin test when examined by the doctor some years ago. He vomited almost at once on eating egg. He did so the second time, then began to have croup. At three he screamed for several hours and had bladder disturbance after eating boiled custard. Now we are very careful, even about ice cream, away from home.

Tommy got very irritable on hot cakes and rubbed his eyelids so that I went to examine the baking powder, and there was dried egg in it. But the new baking powder seems to be made from grapes, and he gets bleary-eyed on drinking grape juice, so there you are.

He walked the floor frantically, holding an ear several times after eating steak, saying his ear had shut up. I sent for the doctor, and his ear had swollen shut. He ate gelatine and his gums swelled like Vincent's angina. He was very sick for a week, had ulcers on his tonsils and bronchitis with a high temperature. He used to clear his throat constantly, and had dreadful itching about the rectum, but recovered when taken off peaches, apricots, etc. He has general prickling when he eats apples.

Possibly this lad's mother was correct when she wrote that he vomited when he first ate eggs. He may have been sensitized before birth. Or he might have become sensitized through breast milk. It has been found that if a mother eats eggs some egg protein may be absorbed into the blood and secreted in her milk.

Tommy appears to have been allergic to grapes. This is not a common sensitization. When it does exist it may cause curious reactions. A lady lives in a part of West Virginia where grapes are grown for wine. She reacts 'positive' to grapes and cannot eat them. After drinking grape juice, grape wine, or brandy distilled from wine, she has hives. During the grape-harvest season each of her neighbours has a small fermenting plant in his back yard. Although she has none in her own yard she has asthma during the harvesting time.

The allergens in alcoholic beverages are not the alcohol, but other ingredients. This is true even of distilled drinks. Some persons can drink Scotch whisky but not rye, and *vice versa.* If a certain man with high blood pressure drinks a Martini cocktail, his pressure rises thirty or forty points. When he drinks a Scotch highball it falls.

Tommy reacted to egg. Eggs may cause many allergic symptoms. A man had a stomach ulcer. The usual treatment gave him no relief. Then he was found to be sensitized to egg. After avoiding eggs he was cured. Other foods may affect an ulcer in the same way. The so-called milk diet has been used for years in the treatment of this disease. Ulcer patients who have not responded to the milk treatment have later been found allergic to this food. Changing to a diet without milk cures their indigestion. Peptic ulcer is not an allergic disease, neither is gall-bladder disease nor appendicitis. But if a person with one of these conditions is also allergic to foods, the foods may exaggerate and prolong the symptoms. In other words, allergy may influence other non-allergic diseases.

The proteins of egg are slightly different from those of chicken meat and of chicken feathers. Patients may have trouble from all three or from only one or two of these three allergens, even though all come from the same animal. The same applies to other varieties of eggs. A man's lips swell each time he eats shad, although he eats shad roe without trouble.

Some Interesting Examples

The condition of the individual may help determine the nature of consequent symptoms. A lady had acne or pimples. She was very highly allergic to beef and to Irish potato. Both produced nausea. Often she vomited after eating either, thus relieving herself of the allergen. When this happened there would be no increased facial irritation. If she did not vomit she would have diarrhœa the next day, together with a new crop of pimples. She had absorbed the allergen.

A feeble-minded girl was paralysed from a birth injury. When she ate chocolate she would have epileptic convulsions. Had she

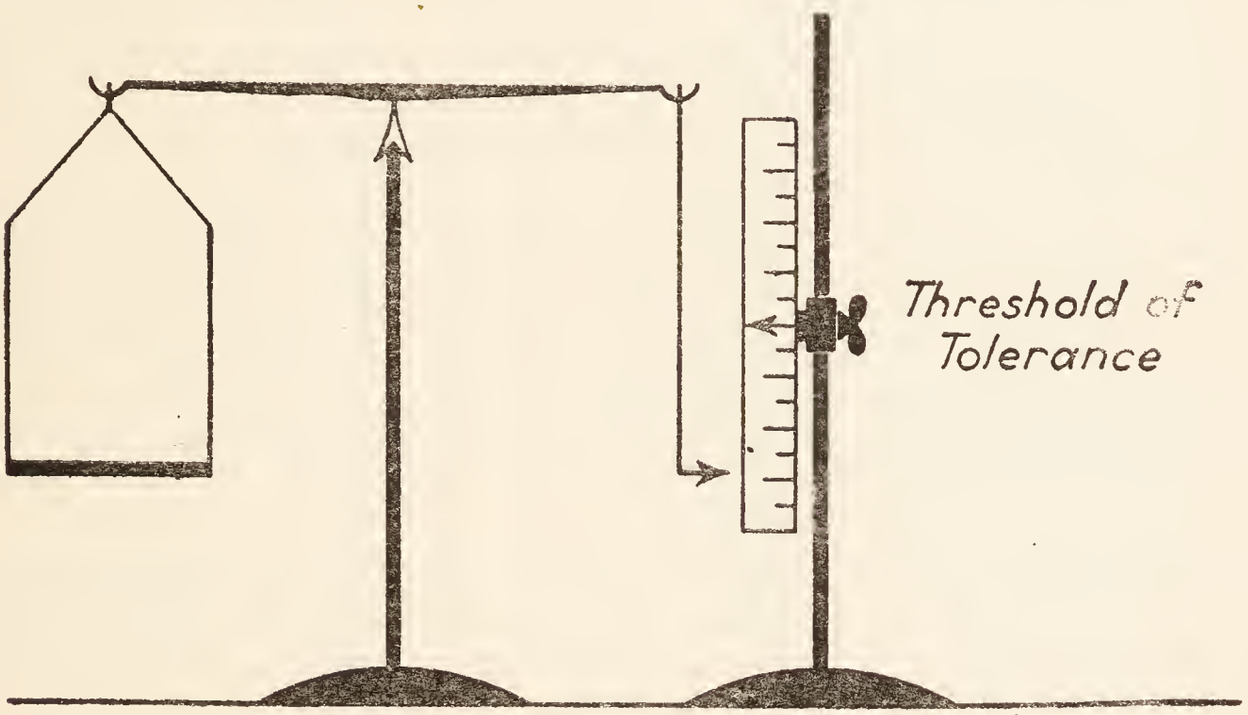


FIG. 13

THE ALLERGIC BALANCE AND THE YARDSTICK OF TOLERANCE

Some persons are so highly sensitized to allergens that even the smallest amount will produce symptoms. Others may tolerate small amounts but develop symptoms if exposed to larger quantities. If one who is exposed to small quantities of a specific allergen does not experience symptoms therefrom, he is in a balanced allergic state or in allergic equilibrium. He will not experience symptoms until the quantity of allergic exposure disturbs the balance to such an extent that his threshold of tolerance is exceeded.

not had the brain injury her allergy to chocolate would probably have taken some other form.

The state or condition of the food may play a part. Some who are allergic to fresh milk can indulge in boiled or canned milk without trouble. A wholesale grocer gets hives when handling crates of strawberries, also after eating fresh strawberries. Cooked strawberries cause him no trouble. A housewife had hives after handling okra in the garden, but not after eating cooked okra.

The soil from which a food is grown may possibly influence its allergenic activity. A man could eat Florida oranges, but not California oranges. A young woman living in Pennsylvania knew

that she could eat Pennsylvania celery, but not celery grown in Michigan. One day she had allergic symptoms after eating celery purchased in a Pennsylvania store. Upon inquiry from the grocer she learned that it had come from Kalamazoo.

Have you ever heard of monkey veal? If the calf has been killed before it is six weeks old, there is enough difference in the quality of the meat for the butcher to recognize. He calls it monkey veal. There is a man who can tell whether or not he has eaten very young veal. It produces sick headache, while more mature veal does not.

A person who is mildly allergic may acclimatize himself or automatically desensitize himself to the offending food. A man reacted mildly to strawberries. At the beginning of the season he had hives each time after eating this fruit. After four or five such daily recurrences he had no further trouble, and could go through the remainder of the season enjoying strawberries.

If, on the other hand, one is rather highly allergic, the condition may gradually become more pronounced after continued eating. A doctor who is very fond of watermelon starts the melon season with just a little discomfort. He says, "I suspect that melons don't agree with me, but the symptoms are not bad, and I am so very fond of them that I continue to eat them." But he gradually becomes less comfortable. "Although I start the season eating melons, I end it not eating them."

The degree or duration of exposure appears to play a part. A woman is allergic to wheat. When she eats bread every day she has much trouble. If she eats it not oftener than twice each week she has little or no trouble.

If one has two or more sensitizations these may interact, causing symptoms to be more pronounced than if only one were acting at a time. A man sensitized himself to chocolate candy by the simple process of eating too much of it. Thereafter he commenced having symptoms from other things, such as lemon and feathers. His allergic threshold of tolerance had been lowered by his new sensitization to chocolate.

A lady is allergic to tomato and strawberry and to sunlight. If she goes out in the sun after eating strawberries or tomatoes, a rash comes out on her arms and neck on those parts which have been exposed to the sun's rays. She may be in the sun at other times, not having eaten these foods, and have no trouble. She can eat strawberries and tomatoes, stay out of the sun and remain symptom free.

A highly allergic person may experience severe symptoms such as Caroline's, but they need not be this same symptom. A doctor allergic to shrimp had quite a different experience. After having successfully avoided it for fifteen years, he ate some by mistake. He didn't know that he was eating it until too late. He became

violently ill with nausea, vomiting, stomach-ache, and diarrhœa. He had a fever of 104 degrees and spent eight days in the hospital.

A lady ate a single cherry. At once she developed angio-neurotic œdema of the mouth, with swelling of the larynx so that she could scarcely breathe. She also had a similar experience after eating blackberry pie.

Concealed Excitants

This raises the question of concealed allergens.

A woman allergic to rice always had trouble at the seashore. She was one of those rare persons who react to but one allergen.

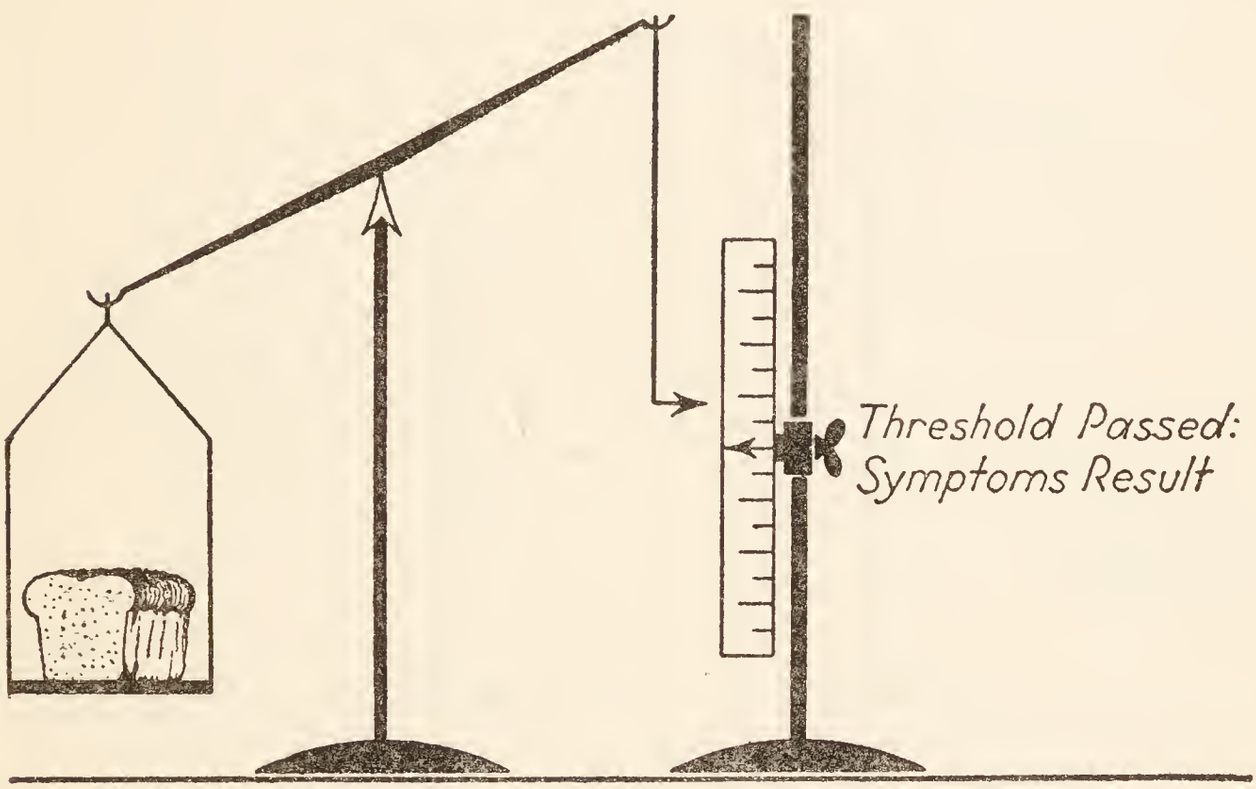


FIG. 14

ALLERGIC EQUILIBRIUM DISTURBED BY BREAD ALLERGEN

This figure illustrates how a large quantity of an allergen, such as bread, may overthrow the balance by exceeding the threshold of tolerance.

Yet she never ate rice at the beach. After several seasons she discovered that rice powder was mixed with the table salt to keep it dry.

If you are allergic to cottonseed, beware of canned tuna fish, since cottonseed oil is often used in its preparation. This may be true of other canned fish. Prepared vegetable shortening usually contains cottonseed. If you are cottonseed reactive, use old-fashioned hog lard. Some salad oils and prepared mayonnaise are cottonseed products. Even olive oil, so labelled, is likely to contain this other oil.

Soya bean is used increasingly in America. It is a perfectly good food, unless you happen to be allergic to it. A man imported soya beans from China. He was soon growing them as his special product. After six years he became sensitized and had asthma

after breathing soya bean dust. When the wind blew from the farm toward his house he became asthmatic. When he ate pork from hogs fed on soya beans he had asthma. Other kinds of pork were all right. You and I may be eating soya bean to-day without knowing it. It is the material that looks like grated peanuts which is sprinkled on breakfast rolls. It is used as an oil in the sweet chocolate industry. Since it retains moisture it is often used in bakers' bread, as it keeps it fresh much longer. The oil is used in some brands of Vienna sausage. This list of its uses is not complete.

A man was extremely reactive to sage pollen. He had moved to a part of the country where there was none. One evening, after

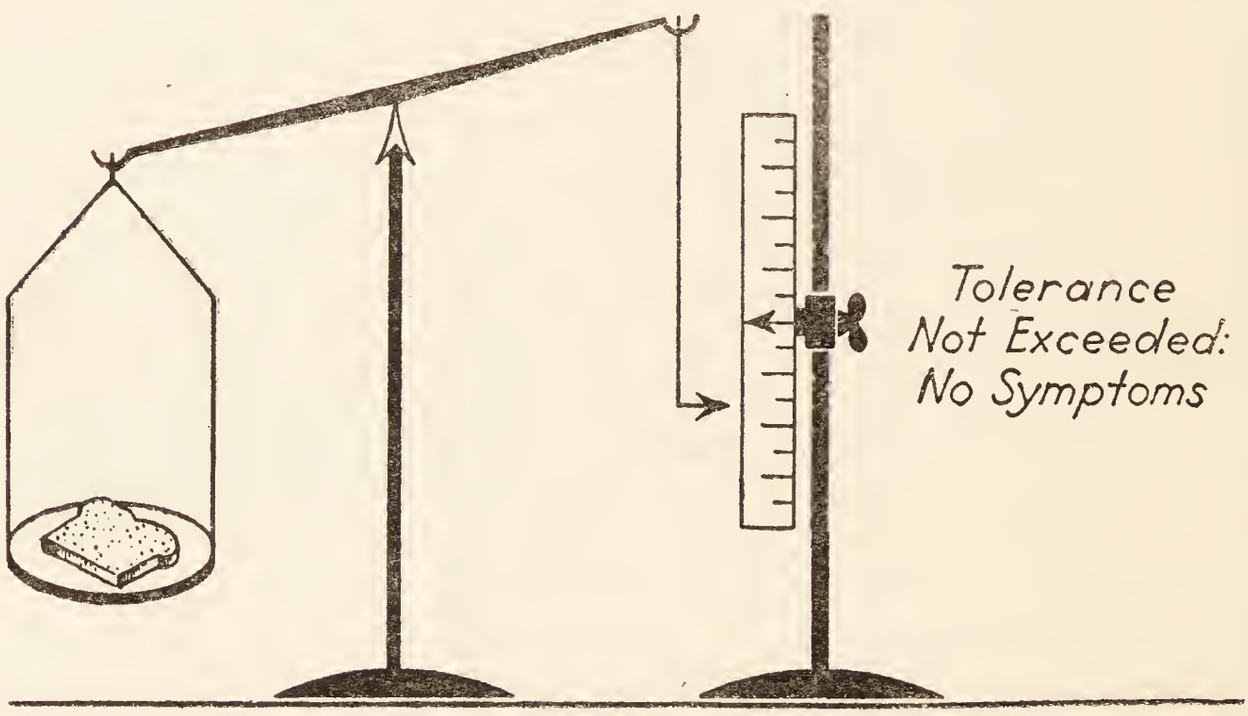


FIG. 15

SMALLER QUANTITY OF SAME ALLERGEN MIGHT BE TOLERATED

The same individual depicted in the preceding figure might tolerate a much smaller quantity of bread without exceeding his tolerance. There is an allergic reaction, as indicated by the tipping of the balance, but the reaction is not sufficiently great to produce symptoms.

eating mutton, he tasted sage so intensely that he dreamed he was once again out West in the sage brush. He had a very real attack of hay fever, presumably due to sage eaten by the sheep, since he was not allergic to lamb. He continued to taste sage for several days. This business of continuing to taste for hours or days is quite common with certain allergic foods.

A Southern U.S. gentleman carried his allergen concealed in his pocket. He had sick headaches only during the hunting season, and even then only after a day's hunt. He didn't know whether it was the birds or the dogs. When tested he reacted to chocolate. Then he realized that although he rarely eats chocolate he always takes along two chocolate bars when going hunting. They are easily carried, don't take much room, and make a filling lunch.

A young boy was allergic to egg. He accompanied his parents to Thanksgiving dinner at the home of relatives. His mother had cautioned their hostess about eggs. Shortly after a delicious dinner the boy went into shock. He was unconscious for three hours. Unthinking, the cook had put egg white in the mashed potatoes.

A man knew that salmon caused his asthma. Although it was served one evening, he ate none. Some of it was kept overnight in the ice-box. When, after breakfast the following day, he had asthma, he realized that the butter had smelled strongly of salmon.

A man had eczema. He reacted to several foods. After avoiding them his eczema cleared up. Then he tried one after another, thus

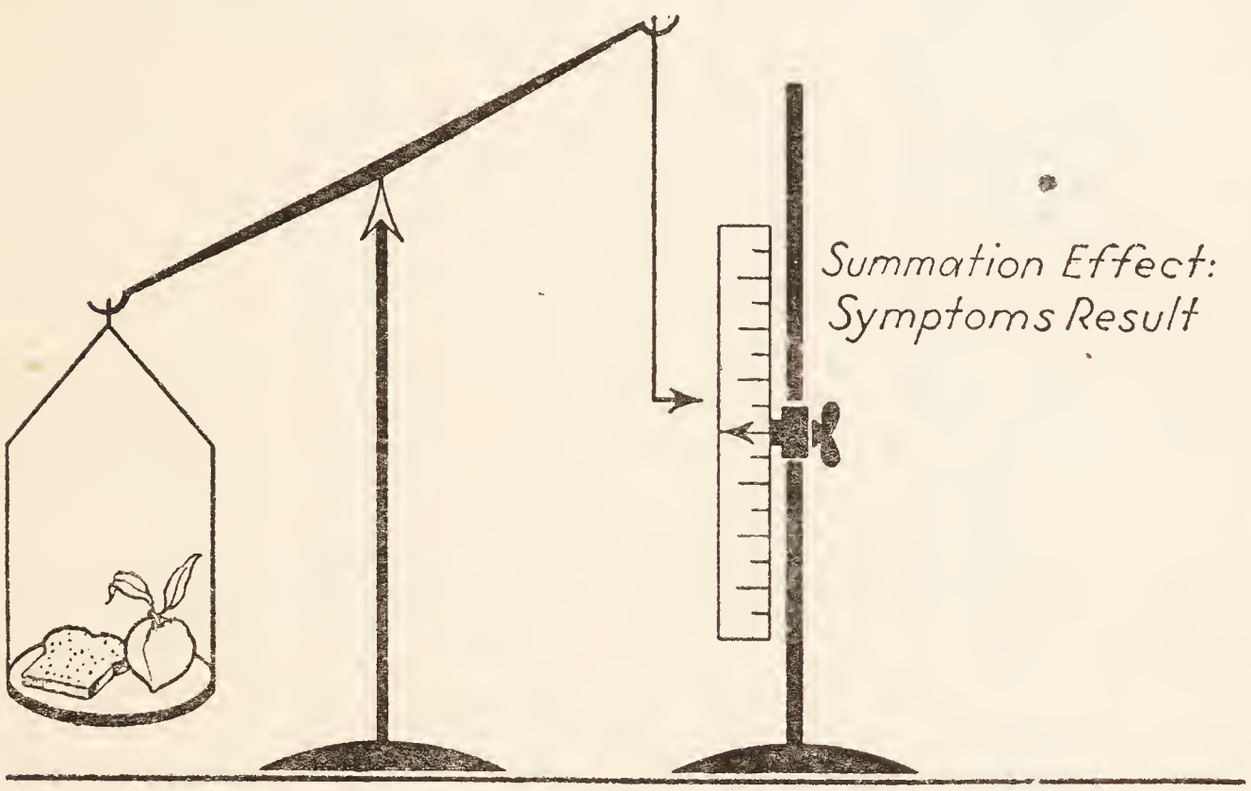


FIG. 16

SUB-THRESHOLD QUANTITIES OF TWO ALLERGENS MAY TOGETHER UPSET ALLERGIC EQUILIBRIUM

A person might be allergic to these two foods and tolerate either one of them in moderation but not both together, even though they are taken in moderation.

establishing that chocolate and lemon caused trouble. As long as he avoided them he was free of eczema. Then he married. During the honeymoon he had an embarrassing return of eczema. He had used a contraceptive containing cocoa butter.

A fireman's wife had hives only when in bed. Contrary to the last victim's experience, she had as much trouble when her husband was away on duty as when he was at home. She reacted to corn. After the laundress stopped starching the sheets she no longer had hives.

Failure of relief is not always due to inability to detect the allergen nor to sensitization to too many foods. The patient may not be co-operating properly. An asthmatic lady consulted her

doctor, who happened also to be a close friend. He found her allergic to milk. Owing to the close friendship he must have been a prophet without honour, for he did not see her again professionally, even though they often met socially. Knowing she still suffered, he wished to study her condition further, but she did not return. Five years later she announced that she had at last cured her asthma. The family had had a cow and she had always drunk large quantities of milk. When they sold the cow she practically stopped drinking milk, and quite miraculously her asthma disappeared. When the doctor reminded her of his earlier advice she replied, "I do remember, but I didn't think you really meant it!" The cure had been too simple. Had the doctor told her to avoid milk and given her a long series of unnecessary injections at the same time, she might have co-operated.

A lady reacted to certain foods. The doctor explained that other foods which failed to give positive skin reactions might also be causing trouble. He told her how to keep a food diary, recording each food eaten and making note of the days on which she had symptoms. When he analysed the diary the attacks always appeared to occur after apple pie. And yet it had been adequately proved that she was not allergic to apple pie. Discussion at last brought out that she invariably had cheese with the pie. She had forgotten to list the cheese in her diary. Without the analytical discussion the cause of her difficulties would have remained unknown.

Some food allergens may remain unsuspected because one would not think of them as foods. Horse meat is an example. A man had served in the French cavalry during the World War. Ten years later he ate horse meat for the first time. He promptly had severe asthma with urticaria. Since then he has had no more horse meat and no recurrence. This is a common food among the poorer classes of Europe. Mare's milk is fed to infants in parts of Russia. Tartar children reared on mare's milk are unusually reactive to therapeutic horse serums. Europeans who can afford better food occasionally find their symptoms caused by horse meat concealed in sausages.

How many of those who like all kinds of cheese realize that in eating Gjedeost, Gorgonzola, Lipton's or Montasio they are probably eating goat protein? Roquefort and several Italian cheeses, Romano, Sardegna, Toscano and Pecorino, are from sheep's milk, although there are imitations made with cow's milk. Latticini is from buffalo milk.

One would scarcely think of glue as a food, but fish glue may cause very severe reactions. One who reacts to fish glue may also react to several species of fish. The glue on postage stamps is made from dextrin, a corn product. That on Christmas seals, envelopes, and various labels is usually fish or animal glue. The lady who has swelling of the lips and tongue after licking envelopes or handling

the wet label on a beer bottle would not consider that her allergy was due to food, but indirectly that is the case.

Christmas Allergy

As a rule Christmas is a bad period for those who are allergic to foods. A lady with urticaria had been doing nicely under treatment. The day after Christmas she again consulted her doctor. She had had a severe attack. At Christmas dinner she had eaten tomatoes. Her philosophy had been, 'Christmas comes but once

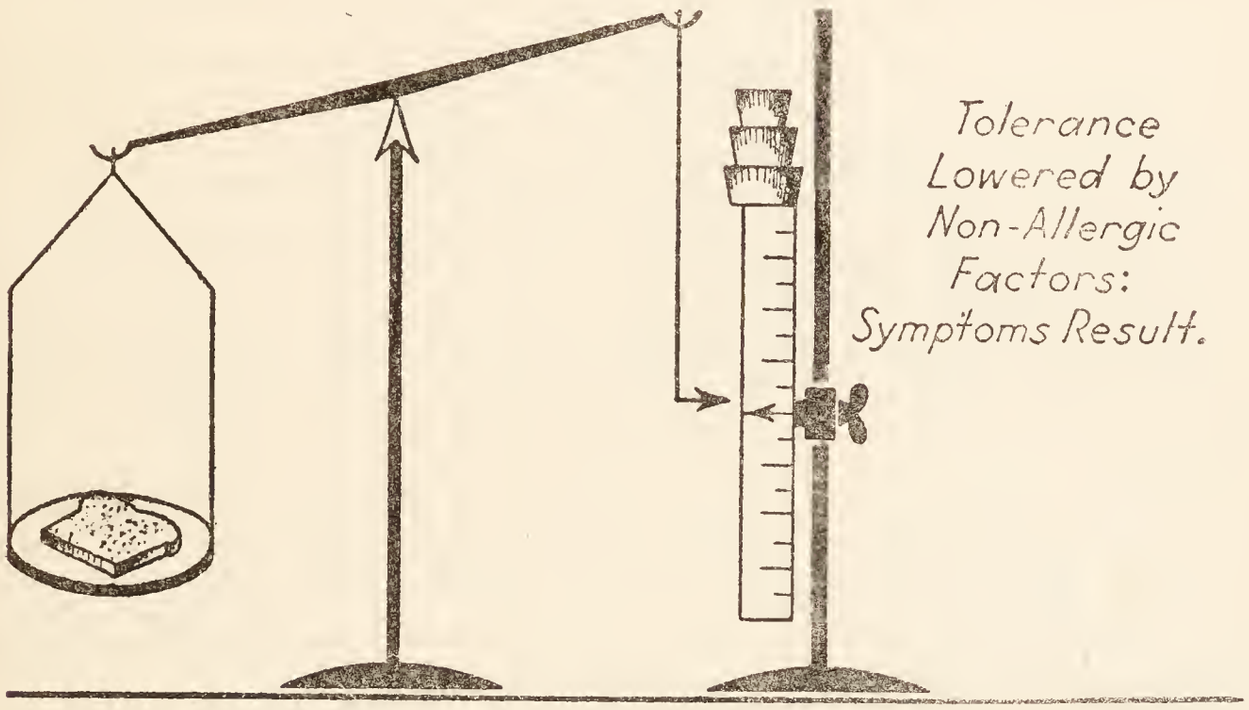


FIG. 17

ALLERGIC AND NON-ALLERGIC FACTORS

A person is allergic to bread. A large quantity exceeds his tolerance (Fig. 14). A small quantity, such as a single slice, does not exceed his tolerance and does not cause symptoms (Fig. 15). One slice may cause trouble if this person's threshold of tolerance has been lowered. Lowering may be produced by non-allergic factors, such as fatigue, excitement, worry, poisoning, constipation, bacterial infection, disturbance of the glands of internal secretion, changes in the weather or chemical factors, such as the inhalation of irritating gases, or mechanical factors, as illustrated in eczema of the neck due to friction from a tight collar. Proper treatment in such cases will include not only attention to the allergenic excitants but also removal of the non-allergic factors.

a year.' This was probably also the attitude of the little boy who ate chocolate. The man who had asthma due to the wheat in his fruitcake probably just didn't think. Some get into difficulty because they over-eat. Even though they may have had no forbidden food, such an overload on the metabolism of predisposed persons may cause return of symptoms. Indirect evidence of the hazards of Christmas was the remark of an asthmatic child's mother. After she had obeyed instructions in spite of the holidays, her mother said that this was the first comfortable Christmas Marian had ever had.

Difficulties at Christmas time are not always due to foods. A

young lady allergic to house dust had severe hay fever each Christmas Eve. At this time she would go to the attic for the tree decorations which had lain twelve long months in accumulated dust. The débutante, delighted with her new cosmetic outfit, a gift from her ardent admirer, or the child, allergic to rabbit hair, with a toy horse whose mane never came from a horse, may show their appreciation by sneezing or wheezing. A few unfortunates have been sensitized to the Christmas tree itself.

Chapter XVI

WINDS BLOWING ILL

RESPONSES TO ALLERGENIC FOODS MAY BE STRANGE, BUT NO MORE SO than those to other excitants.

One might reason that all that need be done for seasonal hay fever is to give injections of pollen extract. The problem is not so simple.

Blackley suspected grass pollen in England, while Morrill Wyman incriminated ragweed pollen in America. But there are many hay-fever pollens in North America besides ragweed. There are three general pollen seasons : an early spring period, due usually to tree pollens ; late spring, due to grasses ; and late summer, when various weeds cause trouble. There are exceptions even to this statement. In parts of Texas and southern California the grasses pollinate practically throughout the year. One may therefore have trouble almost continuously. Ragweed causes most of the trouble east of the Rocky Mountains, but very little along the Pacific coast. Oaks and elms are two most important hay-fever trees in the East. Cottonwood is the chief tree offender in the upper Rio Grande Valley. Although El Paso is on the same river, there are proportionately more ashes planted in the city as shade trees than cottonwoods, and in this locality ash is the chief cause of tree pollinosis. Even the seasons vary in different localities. The mountain cedar which causes much pollinosis in Texas pollinates at Christmas time. While most elms pollinate in the spring, there is a fall-blooming elm in the south-west.

Even among the closely related grasses some variation must be considered. Timothy and June grass are offenders in the northern States, while Bermuda grass and Johnson grass are far more important in the South.

Pollen Carried on the Wind or by Insects

In general, light pollens carried from plant to plant by the wind are important. Other pollens, transported by insects, those

of the brightly blossomed, nectar-scented trees, weeds and flowers, are heavy and sticky, never being carried far on the air currents. However, a surprisingly large number of persons are allergic to these latter pollens and find themselves in difficulty if too intimately exposed.

A man develops hay fever for a week or two each spring only after walking along a certain street. When he follows another route he avoids difficulty. The street is lined with catalpa trees,

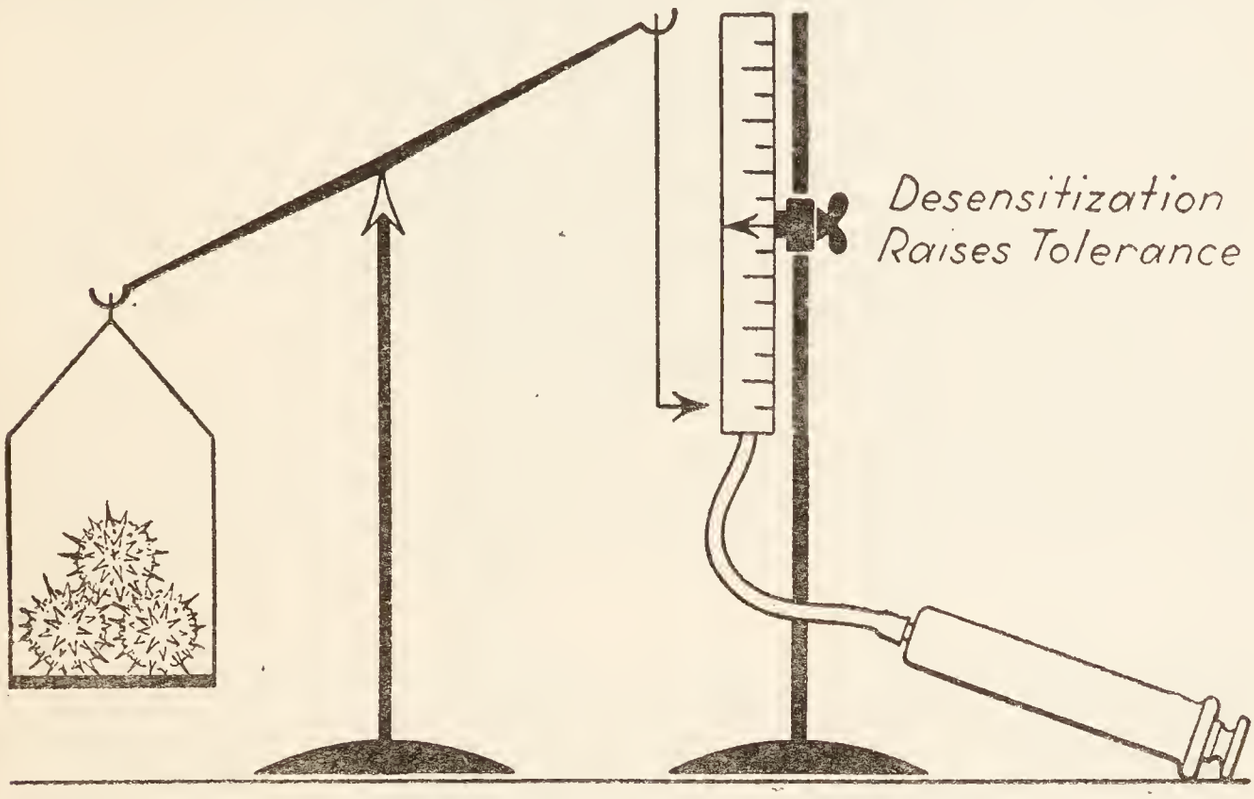


FIG. 18

A LARGER DOSE OF POLLEN WILL BE NECESSARY TO EXCEED THRESHOLD

We may look upon desensitization or immunization against pollinosis as a process of raising the tolerance so that a larger exposure to atmospheric pollen will be required before the threshold is passed. Presumably, this raising of the threshold is accomplished by the production of larger numbers of free-floating protective antibodies (Fig. 10–E)

and his doctor finds him allergic to catalpa pollen. This plant is insect-pollinated.

A lady is allergic to pecan pollen. There is a large pecan tree outside her bedroom window. While dressing she inadvertently put her handkerchief on the sill of the open window. When, later, she used the handkerchief, she developed severe hay fever.

Privet is widely used as an ornamental hedge. Although insect-pollinated, it is near homes and causes many isolated cases of pollinosis. The Chinese are said to have recognized privet (ligustrum) as a cause of hay fever many generations ago.

Cut flowers in the home often cause trouble. In 1868 a doctor wrote : 'For some years I remained at home on account of my asthma attacks. When I was almost well I received a visit from two friends who doubted my word as to the origin of my disease. There-

fore, one of them brought with him a bouquet of flowers and shook it about the room before I appeared, in order to distribute the pollen in the air. As I entered the room I began to sneeze violently, and was seized by an asthma paroxysm that lasted fifteen hours.'

You might think that an ocean voyage would enable one to avoid pollen. A lady had hay fever in mid-ocean, especially when in her cabin. The cause was traced to withering roses. Seventy years ago a doctor told of a hay-fever victim on a sailing vessel far from land. When sails which had not been used since leaving port

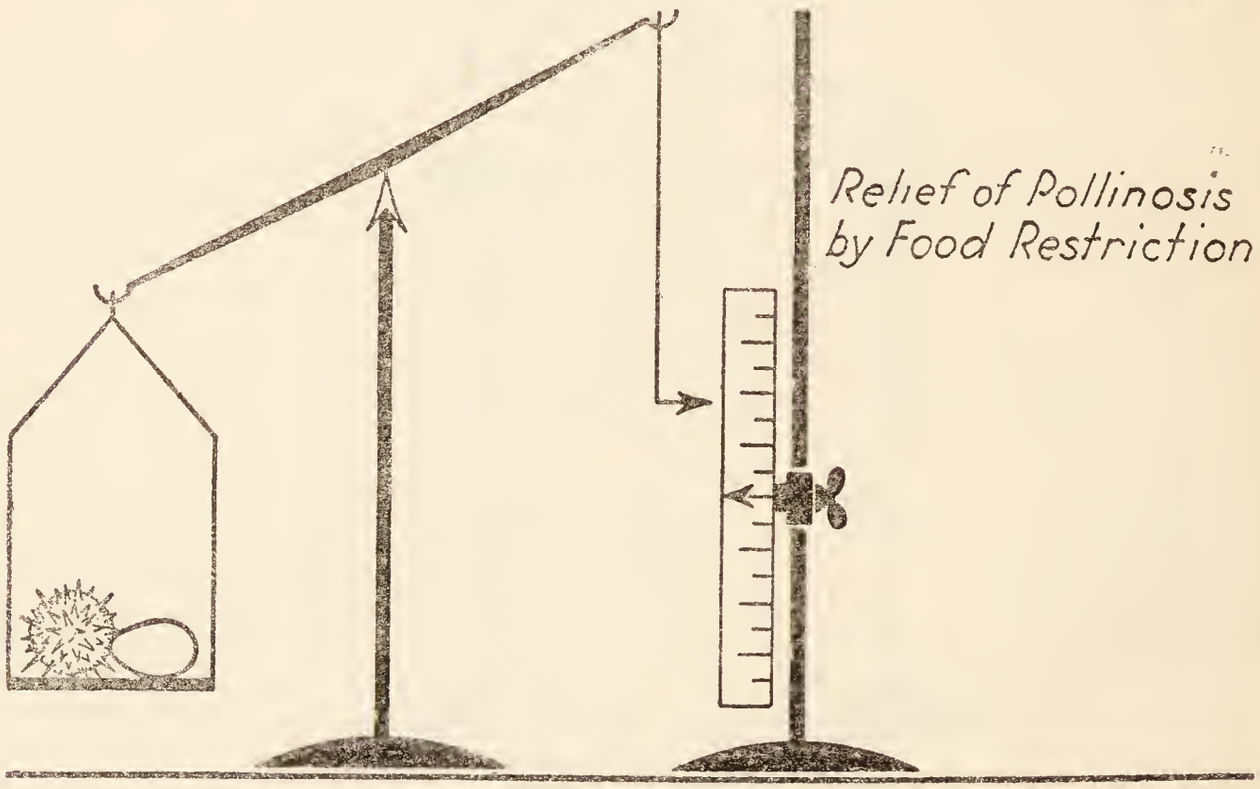


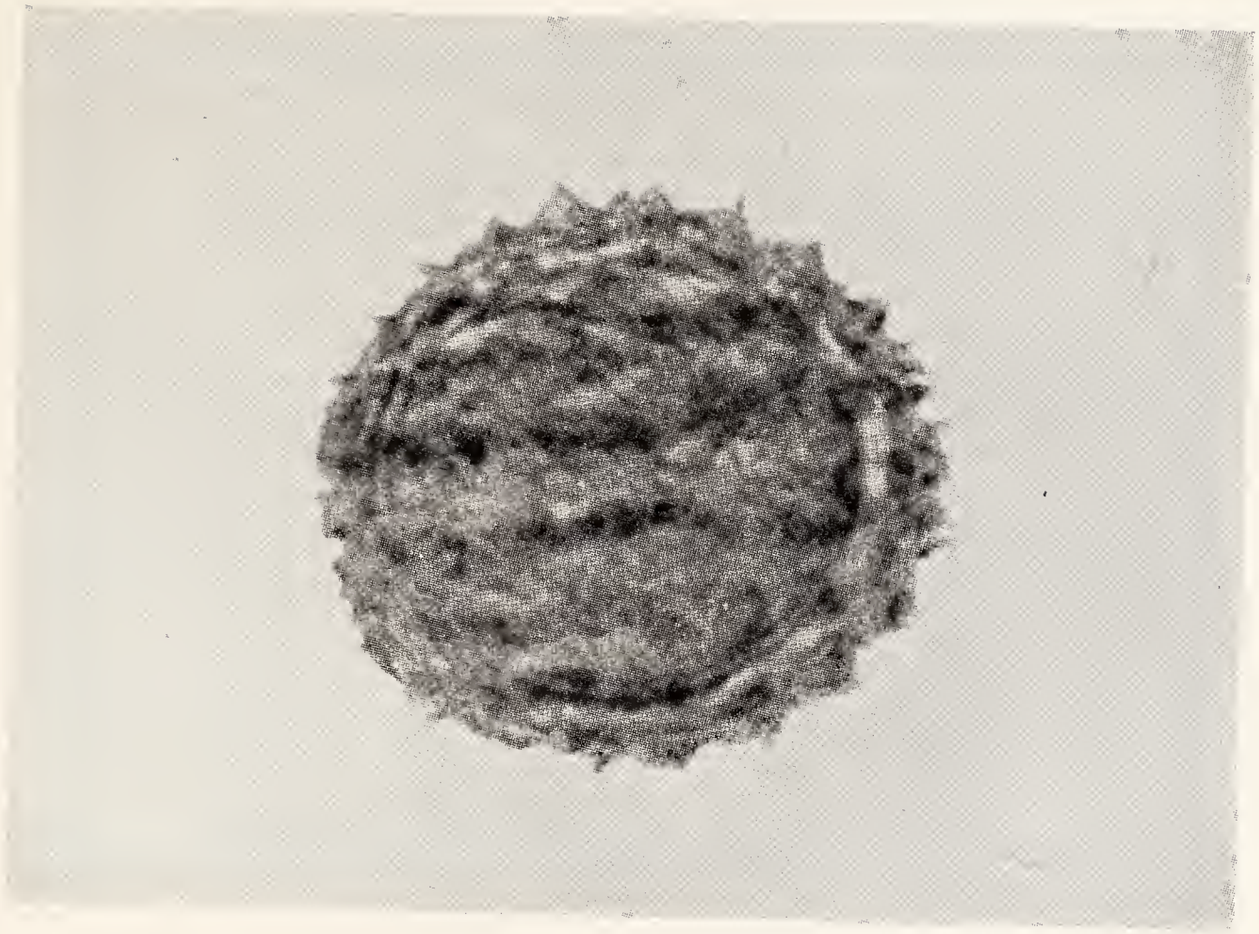
FIG. 19

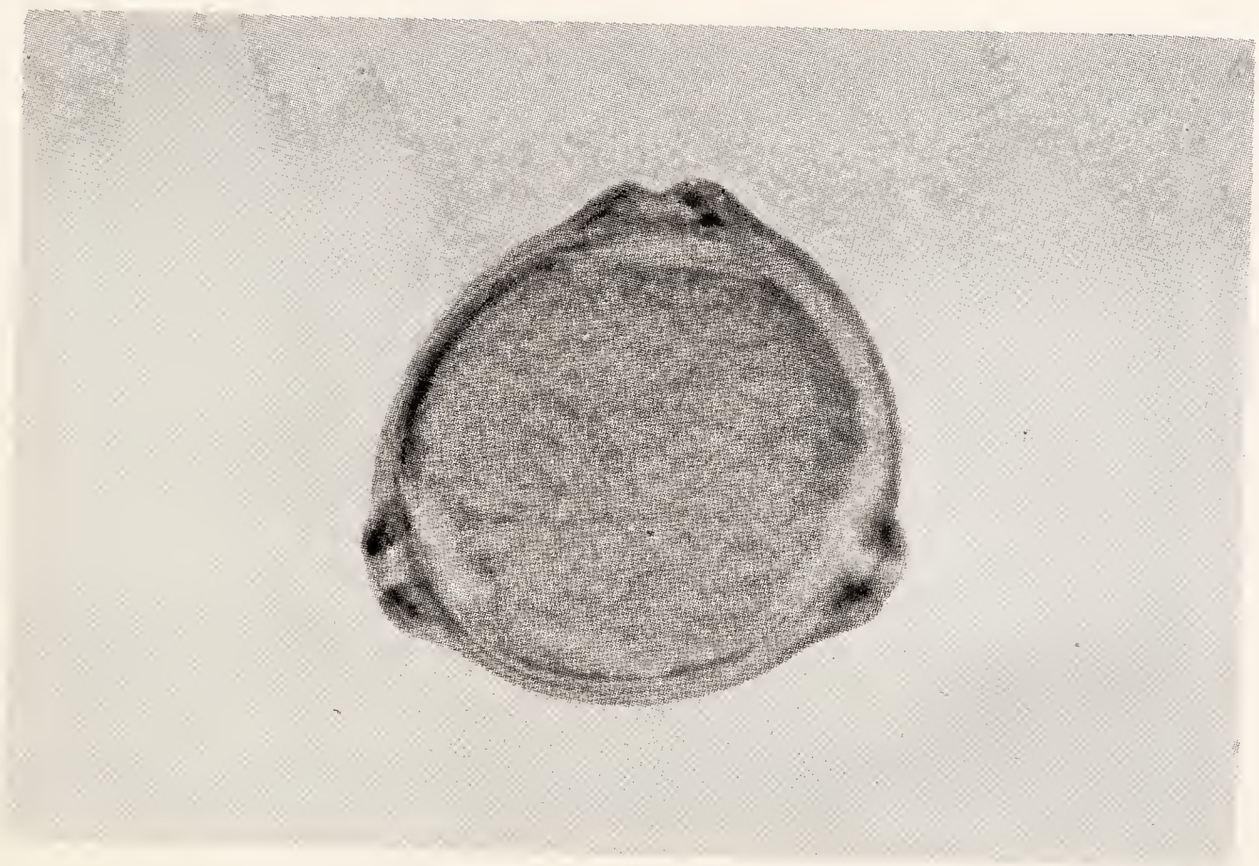
A PERSON ALLERGIC TO POLLEN AND EGG MIGHT RE-ESTABLISH TOLERANCE BY AVOIDING THE LATTER

Many persons with hay fever state that they can eat certain foods at any time of year except when they are having hay fever.

During the pollen season these foods either increase their hay fever or cause some other allergic symptoms. The above illustrates how the addition of pollen disturbs the balance, with consequent exceeding of the threshold. Conversely, a person who is mildly allergic to egg or other food, having no symptoms therefrom except in the pollen season, may improve his tolerance to pollen by avoiding egg during the pollen season.

were unfurled he had an attack of hay fever. Pollen had been released in the dust on the canvas. As a rule, however, an ocean voyage gives relief. George Gray tells of a New Yorker who, during two pollen seasons, leased a room on the Bermuda boat, spending but two days of each week in New York. He was adequately relieved except when on shore. The third year he installed pollen filters in his home and office, again passing a comfortable season. If for some reason desensitizing treatment cannot be given, pollen filters are worth trying. They have the disadvantage that one must remain with the protecting filter. Air conditioning sometimes gives relief.





POLLEN GRAINS

The distances to which wind-borne pollen may be carried are astonishing. Tree pollen has been found in sufficient abundance to cause trouble thirty-four miles from land. Ragweed pollen has been found over the middle of Lake Michigan in almost as great abundance as over Chicago. Grass pollen has been caught in aeroplanes at an altitude of seventeen thousand feet. There may be clouds of pollen, the concentration being denser at 4,000 to 6,000 feet than near the surface of the ground. These result from air currents. In 1873 there was a shower of pollen in St. Louis which made the ground appear as though sprinkled with sulphur. It was believed that this pine pollen had been carried four hundred miles. Similar showers have been described elsewhere. A single ragweed plant may produce eight billion pollen grains per square foot of field surface during the active period of its pollination. An average city lot overgrown with weeds may produce one hundred ounces of pollen in season, which would amount to sixty pounds per acre. Probably a million tons of ragweed pollen are produced in the United States each season.

This enables one to understand why no student flyers who have asthma or hay fever are accepted in the United States army.

Attempts at weed control have failed. In Chicago in 1933 twenty-five thousand men were put to work eradicating weeds. Although one hundred and sixty-five thousand dollars were spent, there was no diminution in the pollen concentration and no lessening of hay fever. With ragweed carried by the wind over fifty or sixty miles of the surrounding countryside, the failure is quite understandable. Similar efforts in Denver and Duluth proved unsuccessful.

With pollens, as with foods, there may be concealed allergens. A man with hay fever due to ragweed had trouble whenever he handled the books in his library, even in winter. The doctor, examining the dust on the books, found pollen grains which had been blown in during the season, and had settled for a year-round stay.

How do the doctors know which pollen extract to use for treatment? By the same expedient used originally by Blackley, very much modernized. You will recall that this pioneer investigator put out microscope slides smeared with vaseline on to which the pollen grains settled. Then he counted them. To-day allergists not only count the pollens each day during the seasons, but also identify the different varieties. They know, from field surveys, what plants which might be causing trouble are pollinating at the time. If the doctor finds box-elder pollen on the slide during just the days when you are having trouble, and if you give a positive skin reaction to box-elder pollen extract, then you should be desensitized against this allergen.

Treatment of Pollinosis

Treatment is, as a rule, very much of a routine affair, giving satisfactory relief to nearly 90 per cent of sufferers. One occasionally encounters curious situations.

Some persons have trouble in only one pollen season, due to tree, grass or weed pollens. Some have symptoms in two of the three seasons, and a few unfortunates are allergic to members of all three groups. In this case symptoms may persist in varying degree from March until frost, although there are usually four or five weeks between the grass and weed seasons when little pollen is in the air and symptoms are in abeyance.

Some persons have hay fever or asthma or both in the several pollen seasons. Others show a strange specificity in their pollen responses. There is a man, for example, who always has hay fever in the spring and asthma in the early autumn. The spring grass pollens never cause asthma, nor does autumn ragweed give him hay fever !

In pollinosis, as in other forms of allergy, desensitizing treatment will usually protect against a reasonable degree of exposure, but not against abnormally large doses. A boy who had had ragweed treatment, and had been nicely relieved until the day school opened in the autumn, rubbed his face with a ragweed plant so that he wouldn't have to go to school. He got his wish. In fact, he spent a week in bed with severe asthma and stayed at home for two weeks because of severe facial eczema caused by ragweed oil.

A lady had had several years of unsuccessful pre-seasonal ragweed treatment. She consulted an allergist. He found her allergic to egg, whereupon she recalled occasional attacks of hives which might have been due to eggs. He told her to avoid eating egg during the ragweed season. The change in her diet relieved her hay fever, even though it was primarily due to ragweed. Two or more pollens or other allergens may interact to aggravate the symptoms caused by any one. Avoidance of eggs was comparable to removing straws to avoid breaking the camel's back. One could leave off the last bundle of straws or remove the first. The result was the same.

This same summation effect is illustrated in the following. A young woman was sensitized to ragweed. She also reacted to pork, mustard and chocolate. She was receiving perennial ragweed treatment, the dose being always the same. Thirty minutes before a pollen injection she broke her diet, eating a pork sausage with mustard and some chocolate. Ten minutes after the injection her eyes became red, she commenced sneezing, and her nose became stopped up. She developed weals at the point of injection. These spread over the entire body. Her nose, eyelids, lips, feet, ankles, fingers, and hands swelled with angioneurotic œdema, and she

developed severe asthma. She was having an anaphylactic reaction. The condition gradually passed. After this experience she remained on her diet, continuing to take the same injections without difficulty.

Pollinosis victims may give positive skin reactions to feathers and house dust, yet sleep on feather pillows and be exposed to dust throughout the rest of the year without symptoms. If such a person, desensitized against his offending pollen, is not adequately relieved during the hay-fever season, he will gain further relief by avoiding feather pillows and being desensitized against dust and feathers during the season. In other words, sensitizations which of themselves cause no symptoms may aggravate symptoms produced by other allergens.

The question is often raised concerning pollen treatment during pregnancy. Although hay fever could scarcely be considered a source of danger at this time, it is a greater potential trouble-maker than is desensitizing treatment. Miscarriages have been brought about by severe hay fever. This is reminiscent of the old country doctor called in consultation by his young competitor in a case of difficult labour. Upon being assured that all of the latest approved methods for facilitating delivery had been tried, the doctor queried, "Have you sneezed her?" Shaking some pepper upon his palm, he waved his hand in front of the lady's face as if he were a magician, and lo, the baby was born!

Chapter XVII

WHAT'S ON THE AIR?

IF THE SYMPTOMS ARE THOSE OF POLLINOSIS, WITH SNEEZING AND stuffy, runny nose, we are likely to speak of it as hay fever, though the illness occurs out of the pollen season or persists through the year. Even when pollen is the cause hay fever is usually an inaccurate term. Ragweeds and roses, moulds and maples are not used for hay, as are grasses, alfalfa, clover, and lespedeza. If symptoms are due to pollens from these latter plants, the term hay is reasonably appropriate. But since fever is not one of the symptoms the second word is inappropriate at all times. Pollinosis is a more rational term.

When you speak of perennial hay fever or hay fever out of season we all know what is meant, but it would be more appropriate to speak of allergic rhinitis or nasal allergy. If the reactive tissue is in the bronchi, with coughing, wheezing, and laboured breathing, we are dealing with asthma.

Dust

Asthma and allergic rhinitis not due to pollen may be caused by a wide variety of excitants. The commonest is house dust. We do not know just what element in house dust causes sensitization. Dust from upholstered furniture, mattresses, and draperies gives stronger reactions than the general run of dust collected in the routine of cleaning. This suggests that the deterioration products of fabrics are important. The older fabrics become, the more brittle they are. Very small, almost microscopic pieces become loosened and become dust. The goods in upholstery and draperies were originally living things : cotton, silk, linen, rayon, horsehair, feathers, kapok, etc.

Symptoms caused by allergy to house dust may be seasonal. They are often worse in the first few cool days of autumn, when windows have been closed and the heat is turned on. Accumulated dust behind the radiators starts circulating in the air of the room. Hot-air heating systems are especially bad in this respect because of the accumulated dust in the air vents.

Trouble from this source may continue through the winter. A seven-year-old boy had severe asthma at home, but only when the hot-air furnace was in use. Relief followed the substitution of grate fires.

Not all house dusts are alike. As a rule, stock dust from any reasonably old dwelling suffices for testing, but many who are 'negative' to this dust may react to dust from their own homes or from furniture in their homes. When this happens it is usually because of some uncommon constituent. A boy's asthma was always worse when he rode in the family automobile. He reacted to dust from the automobile upholstery. He was also allergic to cottonseed. His father's office was in a cotton products mill, and the car usually stood near the mill where cotton dust settled upon it.

A man ordered an ancient book from a distant library. When he opened the package his asthma commenced. He put the book away, had it dusted, and tried again, but without success. After several attempts he returned the book unread. Library dust may contain microscopic bits of leather, glue, old paper, and more moulds and fungi than many other dusts.

One who is highly allergic to dust may be conscious of its presence even though in too little concentration to cause rhinitis or asthma. One doctor, allergic to dust, checks the efficiency with which his patients have rid their rooms of the allergen by going there himself. As he stands in the room his nose informs him whether the job has been well done.

Feathers

Next commonest among the non-seasonal inhalant allergens come feathers. All you need do to prove that old feathers become brittle and make dust is to shake a pillow in a beam of sunlight as it comes in through the window. Much respiratory allergy is worse at night. Usually this is associated with sensitization to the feathers of the pillow on which one's head is resting. We spend approximately a third of our lives, eight hours of every twenty-four, with our noses quite well buried in pillows. Fortunately, dustproof pillow covers are now available.

And Kapok

Kapok is a distant cousin of cotton. It grows in pods on a large tropical tree. Kapok is often used in place of feathers in upholstery and pillows. Because it absorbs water very slowly it is used in life-belts. There are few homes in which no kapok can be found. Some years ago kapok pillows were widely used as substitutes by those who were allergic to feathers. Then we found that kapok is highly allergenic, and that prolonged exposure eventually causes sensitization to kapok as well as to feathers. For this reason dust-proof pillow covers are preferable to kapok pillows.

Experience has shown that persons who are allergic to dust should have no upholstered furniture in their rooms, especially the bedroom, and should use only washable curtains and rugs. The patient who ignores his doctor's directions in this regard courts possible trouble. A woman consulted a doctor in a distant town. He found her allergic to dust, feathers, and kapok. Although he gave her the usual instructions, she was not relieved, and continued to have trouble, especially when in her bedroom. Some months later she wrote with great glee that she had cured herself. She had had a studio couch in her bedroom and, deciding to rearrange the furniture, moved it into another room. Like magic she was freed from asthma. Most studio couches are stuffed with kapok, and the doctor, being far away, had been unable to determine whether his directions were being followed out. Persistence of symptoms is often due to similar failures to comply with instructions.

Sleeping on feather pillows may cause other symptoms than rhinitis and asthma. One man always awakens with a headache. A dustproof cover prevents this. Eczema involving one or both ears has at times been traced to pillows. This is an example of contact dermatitis.

Feathers may be found in other localities than pillows. One man who very carefully used a dustproof pillow cover visited friends in the country. They were transferring two hundred chickens from an old henhouse to a new one. He offered to help. He spent three days in bed.

A lady, equally careful about her pillows, had attacks of sneezing at breakfast. She was wearing a négligée with coq-feather trimming.

Even though her mother had bought her a kapok pillow, a young lady continued to have asthma at night. Although it had been purchased several years previously in a famous Fifth Avenue store and was guaranteed pure kapok, the pillow was found to contain a mixture of kapok and feathers. An allergic individual must always be a doubting Thomas, especially when purchasing materials from places which have not been investigated and vouched for by the doctor.

A lady became quite indignant when informed that her trouble was due to feathers, and that she must cover her pillows. She never used pillows. Each evening, when retiring, she removed the pillows, placing them on a chair. She did not realize that enough feather dust would sift down on to the sheet during the day to give trouble at night, even though the pillows were gone.

Orris Root and Cosmetics

Orris root is another important allergen. This is obtained from a variety of iris grown in northern Italy and southern France. There are several reasons why orris root has, until recently, been widely used in face powders. It has a pleasant, violet-like odour. It acts as a mordant for other perfumes added to it, retaining their gentle fragrance for a long period. It is flesh-coloured, and clings to the skin better than most other powders. So many are allergic to orris root that a large number of cosmetic manufacturers have discontinued its use.

A sea captain had asthma when on his ship, and practically never when ashore. Allergic to kapok, he was sleeping on kapok pillows. His case was the reverse of that of another captain who remained well when at sea, but invariably had asthma within a few hours after reaching any port. He was sensitized to the orris root of milady's cosmetics.

Orris root is used in beauty parlours for dry shampoos. A beauty parlour operator had asthma due to powdered orris root. Since she did not react to buckwheat flour the doctor advised her to use this in her work. Ten months later asthma returned. She was then found reactive to buckwheat, but she did not react to rye flour. So she used rye flour for the shampoos. A year after this, when asthma returned, she reacted to orris root, buckwheat, and rye. Barley and rice flours being negative, she changed once again, using barley flour. Some persons tend to become sensitized more easily and more rapidly than others, but in this case the extreme degree of exposure in her occupation played a great part.

Pyrethrum

Pyrethrum of commerce is the powdered petal of a variety of chrysanthemum. It is widely used in insect powders and sprays and causes much sensitization. Fortunately, effective insecticide powders and sprays which do not contain pyrethrum are available.

A man with hay fever due to ragweed, who was also allergic to pyrethrum, found relief in the ragweed season by remaining in his air-conditioned apartment. One day, for no apparent reason, his symptoms returned. He investigated. There were cockroaches in the cellar several floors below, and an insect powder which contained pyrethrum had been distributed lavishly about the basement. Some had permeated the hallways.

Silk

Sensitization to silk is not uncommon. When it occurs it is usually due to the inhalation of particles of silk dust.

Tobacco

Tobacco is a rather common cause of inhalant allergy. Those who are highly reactive need only to breathe the air where others are smoking. I have said that humans are not allergic to each other. Had it not been for her positive tobacco reaction, it would have been hard to convince a certain lady of this. She had perennial asthma due to several substances, but it was always worse when she slept with her husband. When he was away or slept elsewhere in the house she was more comfortable. True, he did not smoke in bed, but enough smoke clung to his skin, and especially to his hair, to increase her asthma. Since she couldn't bring herself to ask him to stop smoking, she took desensitizing injections of tobacco-smoke extract. Thus was domestic happiness restored.

Nor are symptoms necessarily respiratory. A lady gets hives when she smokes. Even when she is not smoking she absorbs enough of the allergen to break out with a rash if she sits for a long time where others are smoking.

One may become allergic to smoke other than that from tobacco. A farmer's barn burned. His wife, helping to lead the livestock out, was nearly suffocated. After recovery she had asthma whenever she sat before an open-grate wood fire. Her doctor tested her with an extract of wood smoke. The reaction was so strong that she went into anaphylactic shock, from which fortunately she recovered.

Animal Hairs

Animal hairs and danders account for much respiratory allergy. Cats, dogs and horses are the chief offenders, simply because exposure to these allergens is more common. Since one doesn't

keep cows in the parlour or ride cows for pleasure we would not expect cattle hair to be as important a factor. Sometimes it does cause trouble, even in the parlour. The heavy padding often used under large rugs to increase their softness contains the hair of many animals, and is usually chiefly cattle hair.

Woollen blankets contribute their share of trouble, and occasionally goat hair in rugs and in mohair cloth causes symptoms. I have mentioned respiratory allergy, which commences or becomes worse with the first cool days, and is caused by dust circulating from the radiators. There are other causes for symptoms commencing at this time of the year, one of which may be the wool blanket which has been stored away during the warm months. It might seem silly to test Americans for sensitization to camel hair, but this may be a constituent of long-fibre 'wool' coats, blankets, sweaters, and Oriental rugs. It is a fine material except for those who are allergic to it.

At times the source of exposure is hard to trace. An asthmatic boy known to be allergic to dogs moved into a home recently vacated by an elderly gentleman and his wife. His asthma returned, persisting as long as he stayed in the house, even though he carefully avoided dogs. Investigation disclosed that the previous occupants had had several dogs, which had had the run of the house. Enough hair was left to cause trouble even though the house had been cleaned prior to occupancy.

Some years ago a doctor placed a cat on an upholstered chair. Cats being as they are, the animal purred and settled down for a quiet nap. After about an hour tabby was removed from the room. A visitor allergic to cat hair was then invited to sit in the chair. He knew nothing of the previous arrangements, but he promptly had asthma.

There is a volatile element in fur and hair which, although too small to see even with the strongest microscope, permeates the air. Were it not for this, dogs could not follow the scent. A doctor believed that this same element was present in urine. He exposed extracts of horse urine in an open dish in a room. Later, he brought horse asthmatics into the room. They responded with attacks of asthma.

This is not difficult to understand if we realize that the odours of perfumes are due to minute particles of the substance being carried through the air and deposited in our noses. Recent investigations in France have proved this to be the case. Powder distributed over quicksilver can be seen to move under the bombardment of small particles of odour. This explains why the courting swain had asthma until his lady love changed her brand of perfume. This might have been another case of supposed allergy to humans. It also explains a lady's sneezing when foods are being fried.

Et Cetera

Tissue handkerchiefs are a boon to those who must sneeze their way through life. One may become allergic to such paper kerchiefs. Too bad for the victim if the situation is not recognized. One may become sensitized to medicines customarily used for relief, such as ephedrine or other nasal sprays. One finds it hard to suspect a medicine which has previously given relief, and usually continues using it, thus aggravating the symptoms.

One may become sensitized to nearly any type of paper. Newspaper is an occasional cause of trouble. A certain man cannot read the Sunday rotogravure without having asthma. He also has asthma after passing a painting plant. Fresh paints and varnishes cause much asthmatic trouble, due usually to linseed oil, a flax seed derivative.

The study of allergic reactions may unearth curious pets. A man living in New York State consulted a physician because of asthma. He reacted to deer hair. To his surprise the doctor discovered that the patient had deer as pets. The man disposed of the animals and his asthma simultaneously.

A well-to-do man reacted to hog hair. Since he had much less faith than his wife in the teachings of allergy he jokingly referred to his sensitization as an example of the uselessness of the procedure. There certainly was no contact with hog hair in his case. A few years later, after he had forgotten the incident, he bought some prize hogs. Whenever he went into the pen he broke out with hives. Recalling his previous positive reaction, he promptly became an allergy enthusiast.

Then there is a vast number of occupational inhalants which may cause trouble. There is a man with asthma from handling formaldehyde, used in making matches. There is the baker asthmatic from inhaling wheat flour, and the miller who has trouble from soya bean dust. There is the carpenter allergic to sawdust, and the jewel polisher with trouble from boxwood dust, the cabinet maker reactive to rosewood dust, and the piano maker allergic to ebony dust. There is the artist whose asthma is due to rubber erasers, and the garage mechanic who is sensitized to some element in exhaust smoke. There is a man who has asthma when he burns soft coal in his furnace, but remains well when hard coal is burned. This list of curious sensitizations is far from complete.

Ultima Thule

One of the first duties of a doctor is to save lives. When his patient is seriously ill he does this to the best of his ability. He succeeds often enough. With his patient again well he settles back, happy in the knowledge that his job has been well done. And yet, with the exception of emergency surgical procedures, it is difficult

for any doctor to say that the patient would not have recovered, anyhow. The probabilities may have been otherwise, but although the doctor is constantly helping toward recovery, it is rarely possible for him to state unequivocally that what he did saved the patient's life, that otherwise the outcome would certainly have been fatal.

Looking at it in this way, I can say that, with the exception of non-allergic emergency procedures, I know of only two lives that I have saved.

One afternoon a doctor called from a distant city, urging me to come as quickly as possible to see a boy who appeared fatally ill with asthma. The lad was in an oxygen tent. If I could not arrive before the morrow, it would be too late. I was at the boy's bedside at about ten o'clock that evening. He showed those symptoms so familiar to doctors and nurses, which told that within a few hours he would be breathing no more. A few skin tests had shown allergy to certain foods. These foods had been eliminated. As a matter of fact he had eaten very little food of any kind during the preceding day, nor was he in any condition for further testing. Although the child had not been tested for sensitization to feathers or other inhalants, his doctor had realized that feather pillows often cause asthma, and had substituted kapok pillows.

Dr. Hyde Salter, wise in the ways of asthma, sixty-five years ago formulated a general rule that asthmatics do best in climatic surroundings which are the reverse of those to which they have been accustomed. He had sent those living at the seashore to Alpine resorts, and had observed that asthmatics from Switzerland were relieved at sea level. The reason was obscure to him, but we know to-day that relief was due chiefly to unconscious escape from some local environment allergen. The patient at the seashore, allergic to moulds, need not have gone to Switzerland. He might have found as much relief by travelling a few miles inland to some new dry abode free from fungi.

I applied the same reasoning in the problem with which we were confronted. If the child's asthma were intrinsic (page 113), he was already beyond aid. If it were extrinsic, the environmental allergen must be found and removed. Here the child was, in a small sequestered world of his own, inside the oxygen tent, breathing the purest of pure air. There was but one thing in the tent with him, the kapok pillow. After an examination, necessarily brief because of the boy's extreme exhaustion, I removed the pillow, leaving him in the tent. With the other consultants we retired to discuss the case. We were gone somewhat over an hour. When we returned the boy was sitting up, calling for water, very obviously on the road to recovery.

The following day we tested him with an extract of kapok. The reaction was positive.

The second case was equally spectacular. I had examined a

young lady, finding her sensitized to several allergens, including feathers. A year later she became acutely asthmatic. Her physician placed her in the hospital under an oxygen tent. From here on the story is almost a duplicate of the first. As I entered the room the three physicians remarked that I was too late. She could not live more than an hour or two. In the tent she was propped up on four feather pillows. We removed these, substituting rolls of cotton blankets.

She still has occasional asthmatic attacks, particularly when travelling in Pullman cars. She has solved this problem in great measure by taking her short trips by bus, her long ones by plane.

Chapter XVIII

STRATOSPHERE ALLERGENS

THERE ARE FORMS OF MATTER IN THE AIR OTHER THAN POLLEN AND dust particles. One of these is spores from fungi, such as the mildew mould, and from other low forms of life. Fungus spores are surprisingly numerous. The air in a room may contain as many as 250,000 spores per cubic yard. Like pollen grains these may be carried long distances. They have been collected in stratosphere flights 36,000 feet above the earth, where the temperature is 78 degrees below zero, centigrade. Winds have blown rust spores from Texas to Minnesota in the short interval of forty-eight hours. Other fungus spores have been blown from Minnesota to New York in twenty-four hours.

As with pollen, one is more likely to be sensitized to the common fungi of the air than to those which one rarely encounters. The common moulds cause mildew on canvas and on the backs of books as well as the dank odour in moist cellars. They turn stale bread green or black and grow on jellies and preserves.

Holland is a damp country where moulds abound. In 1925 a Dutch doctor was searching for the cause of a lady's asthma. Since she reacted to feathers he prescribed a kapok pillow. Her asthma was relieved. After some time she again consulted him, for her symptoms had returned. Presuming that she had now become sensitized to kapok, he tested her, but she was negative. He then made an extract of her own kapok pillow, to which she reacted strongly. Why was her kapok pillow different from other kapok pillows? He found the answer in a mould growing in the fibres. From this beginning Dr. van Leeuwen investigated fungus allergy in Holland, finding it very common. Other investigators in Spain, Germany, England and the United States confirmed his findings. Mould allergy is more common in damp climates.

Although 16 per cent of German asthmatics react to fungi, 53 per cent do so in more humid England.

In the United States this form of sensitization is commoner in sea coast towns than inland, although there are certain exceptions. Some fungi require less moisture, and these may cause trouble in the interior. Alternaria, which grows on wheat and is abundant in the north central section of America, is the outstanding example.

In Galveston the frequency of asthmatic attacks depends in part on the direction of the wind. When the wind is from the marshy mainland the spore counts are high and asthma is active. With a south wind from over the Gulf of Mexico mould counts are low and there is less asthma.

A doctor in a Florida city could not relieve his mould-sensitized patient until after he had inspected her bedroom. There he found a mildewed awning at one of the windows. The awning was removed and her asthma was relieved.

Lycopodium is a yellow powder consisting of the spores of a kind of moss. It was formerly used more extensively than now, chiefly by druggists as a dusting powder. Pills rolled in lycopodium stayed dry and did not stick together. Years ago lycopodium was used on the stage, especially in France, when either rain or fire was required. The spores burn rapidly, with a brilliant blaze, leaving no smoke and no danger from burning embers. When rain was called for, the powder was sprinkled from above. Consequently there was much lycopodium in the dust of theatres. During the last century there were asthmatics who could not attend the opera because of lycopodium. This is one of the few allergens that have ceased to be important.

Spores from other plants may cause trouble. A man found that he had asthma when sitting in his room next to an asparagus fern. He was relieved when the fern was removed.

One may experience difficulties from eating fungi. Mushroom is the important representative of this group. The flavouring of many cheeses is dependent on fungus growth, which is also responsible for the green colour of Roquefort. Yeast is a variety of fungus which we eat in bread and drink in wines and beers.

And Down to Earth

Some fungi have the power of infecting the skin. Common 'athlete's foot' is a fungus infection, usually of the foot and involving especially the warm, moist areas between the toes. Trichophyton is a common infecting mould. A somewhat similar type of skin infection, more prevalent in children, is due to monilia albicans, a yeast-like organism.

The local infection is only part of the story. One may become sensitized to these moulds as they grow in the skin. When this happens the patient develops one or another allergic symptom

elsewhere than in the infected area. The commonest is an eczematous lesion on the hands or arms. In such cases one must not only treat the local infection but also give desensitizing injections.

Athlete's foot, more properly called epidermophytosis or trichophytosis, is a city dweller's disease. Wherever a person with the disease puts down his bare feet some of the fungi are deposited. The bathtub, the bathroom floor, the locker room at the club and the carpet in the hotel bedroom are some of the places where the enemy lurks unseen. As a rule cure of the infection is not difficult, but reinfection from sources such as those just mentioned is almost certain. If, having been cured, one would avoid reinfection, it would first be necessary to destroy every pair of shoes and slippers and purchase a new outfit.

A Southern U.S. gentleman had trichophyton infection of the feet and, because he was allergic to the fungus, he also had asthma. Local treatment cured the infection, while desensitization with an extract of trichophyton relieved his asthma. He used every precaution to prevent reinfection, and neither symptom returned.

Later, with the opening of the hunting season, he absentmindedly put on an old pair of mouldy hunting shoes that had been in the attic, unused, for nearly a year. As a consequence of his single day of hunting he had to endure a return of the infection between his toes and a return of his asthma. With treatment he was again relieved. Needless to say, he purchased a new pair of hunting shoes.

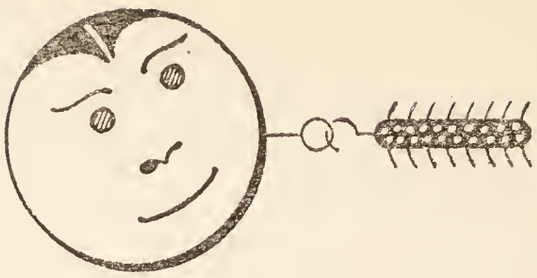
Chapter XIX

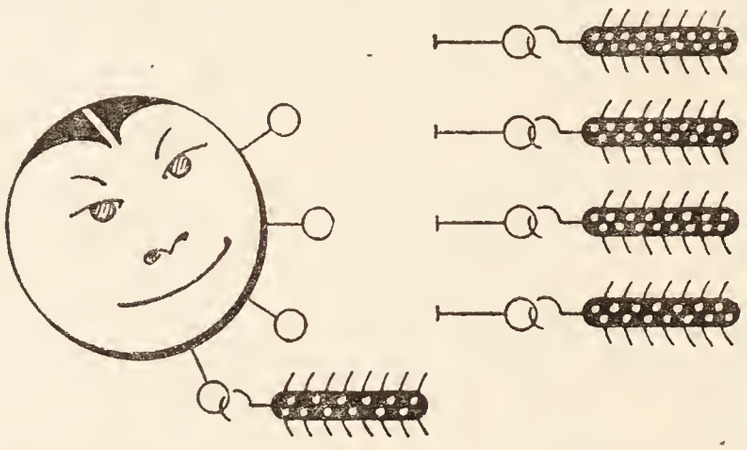
TROUBLE FROM WITHIN

ONE MAY BE ALLERGIC TO BACTZRIA. WHEN THIS HAPPENS TREATment may be difficult, because the offending allergen is living within the body and avoidance is consequently impossible. In such cases one must depend primarily upon desensitization, with the knowledge that continuous exposure to the allergen may interfere with satisfactory results. When the allergenic germ is in a focus of infection and this focus can be removed results are better. This probably explains occasional relief from asthma or hives or angioneurotic œdema after tooth extraction or the removal of diseased tonsils, gall bladder or appendix.

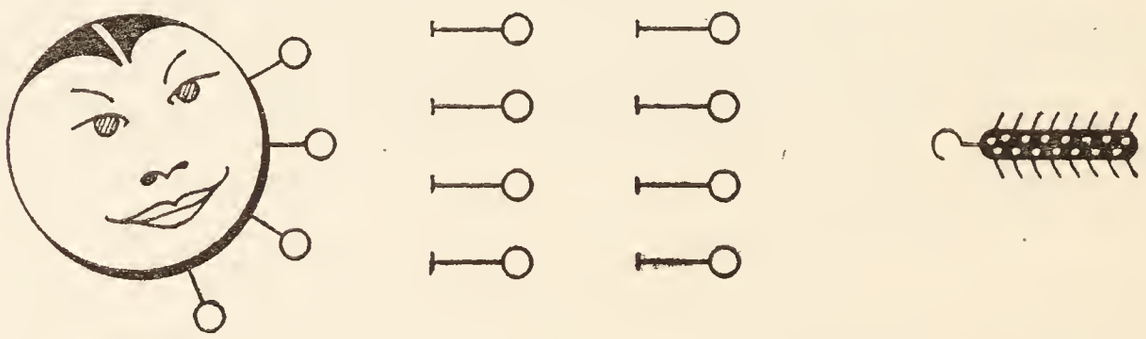
Extrinsic and Intrinsic Allergens

Until now we have discussed responses to allergens originating outside the body. We must also consider factors acting from within. Bacterial infection and, occasionally, disturbances of the glands of internal secretion are in this category.





IMMUNIZATION



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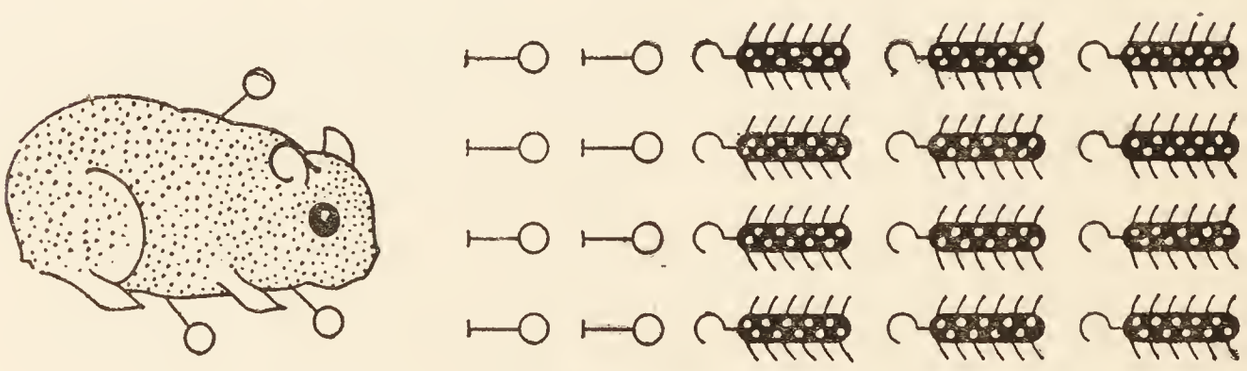

SHOCK

FIG. 20

THE DIFFERENCE BETWEEN HUMAN IMMUNIZATION AND EXPERIMENTAL SENSITIZATION

We speak of extrinsic allergy and intrinsic allergy. In the former the excitant is normally outside the body, causing trouble only after penetration. If its entry into the body can be prevented, reactive symptoms subside. If, as in the case of pollen, its penetration cannot be prevented, there is still the possibility of successful treatment by desensitization. It is not an easy matter to eradicate bacterial infection, the chief factor in intrinsic allergy. As a consequence treatment is not always successful.

In many cases both extrinsic and intrinsic factors play a part. Asthma may be caused by sensitization to house dust. Avoidance and desensitization may give some relief, but infection hidden in the sinuses may interfere with completely satisfactory results. The obvious procedure in such cases is to try to eradicate the infection, too.

One need not be sensitized to the infecting bacteria. The existence of infection may itself suffice to cause symptoms.

It should not surprise us that persons may become sensitized to bacteria, since the Ehrlich side-chain theory was developed as an explanation of bacterial immunity and its application to allergy was predicated upon an identical mechanism. Much of the early investigative work on experimental anaphylaxis was done with bacterial protein as the antigen. Guinea pigs were sensitized

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FIG. 20

THE DIFFERENCE BETWEEN HUMAN IMMUNIZATION AGAINST TYPHOID AND EXPERIMENTAL SENSITIZATION TO THE TYPHOID BACILLUS

Top panel : In both processes dead typhoid bacilli are injected, thus sensitizing the cell and causing the production of typhoid antibodies. It should be borne in mind throughout these illustrations that, as stated under Fig. 3, all antibodies have been shown as looking alike. This is for simplification. The typhoid antibody is different from horse-serum antibody or egg antibody. All specific antibodies differ from all others.

Second panel : In human immunization (three injections, at weekly intervals, of increasing quantities of typhoid protein) human cells have been stimulated to produce increasing quantities of protective antibodies.

Third panel : When one drinks water containing typhoid bacilli only a very few of these living germs pass through the walls of the intestine into the blood. There they meet protective floating antibodies and are damaged by combining with them. This kills the typhoid bacillus before it can reproduce and grow to any large numbers.

Fourth panel : When we produce anaphylactic shock in guinea pigs with injections of typhoid vaccine the same process takes place as in the first and second panels. The difference is in the third and fourth panels. An immunized patient infected with the typhoid bacillus has sufficient floating antibodies to protect himself. But when typhoid vaccine is injected into the guinea pig's blood such relatively tremendous quantities of typhoid protein are introduced that there are not enough floating antibodies to protect the animal cell. In the illustration the first two ranks of approaching typhoid bacilli will be neutralized by the two protective ranks of floating antibodies. This will leave a third rank of typhoid-bacillus protein to combine with the attached antibodies of the guinea-pig cell, thus producing damage to the latter and anaphylactic shock.

It should be understood that this and all similar illustrations in this book show how immunity and sensitization or anaphylaxis might be produced in terms of the Ehrlich side-chain theory. It should also be understood that the side-chain theory and the histamine theory are not the final explanation. They are the most intelligible explanations that we have at present, but will undoubtedly be modified after we learn more of allergy.

against typhoid-bacillus protein injected through the skin as a vaccine. After ten days or more, reinjection of the same vaccine in suitable dosage caused death from anaphylactic shock.

Prophylaxis v. Anaphylaxis

You may ask how this fact can be reconciled with the injection of typhoid vaccine to protect people against typhoid fever. The answer is not difficult.

Man receives three injections of protective typhoid vaccine at weekly intervals. Seven days is too short for the development of clear-cut sensitization. By the injections the cells are taught to produce free, protective antibodies.

During the second injection after ten days of typhoid vaccine into the sensitized guinea pig typhoid protein combines with free antibody. Its attraction toward the living body cells is thus neutralized, just as it should be for protection. But the guinea pig is a very small animal, and we have given him a tremendous dose as compared with what we use when vaccinating human beings. There is too much typhoid protein in the second injection. There are not enough free antibodies to completely neutralize it. That which remains becomes attached to the tissue cells, thereby causing injury. It is primarily a matter of the quantity of antigen administered.

A human being vaccinated against typhoid drinks contaminated water containing a few living typhoid bacilli. In an unprotected person these few bacilli will grow in the blood in great abundance. But when the same few enter an immunized vaccinated person they combine with free antibody and are thus destroyed. They might even combine with attached antibody but are numerically so few that the damage is negligible.

The combination of typhoid protein with human protein through the antibody as a connecting link injures the latter as well as the former. The process works both ways. The typhoid cell is injured and cannot grow. If only a few body cells are injured at the same time, there will be no symptoms, and since the germs are destroyed in the same reciprocal reaction, immunity results.

If very large quantities of antigen are injected, large numbers of body cells are damaged in the process of destroying the antigen. The result is anaphylaxis.

How do we know that persons may become sensitized to bacteria? First we have the experimental proof of sensitization in animals, just discussed. Second, many allergic persons give positive skin reactions when tested with bacterial vaccines. Third, they sometimes respond satisfactorily to desensitizing treatment with vaccines. Fourth, once in a while a person will react to an extremely small dose of vaccine in such a violent manner that it can only be explained as due to allergic shock.

As an example, a man was being skin tested with a streptococcus vaccine. Scratch test was negative. An intracutaneous test was then made, the material being injected from a hypodermic syringe directly into the skin. This test is roughly one hundred times more

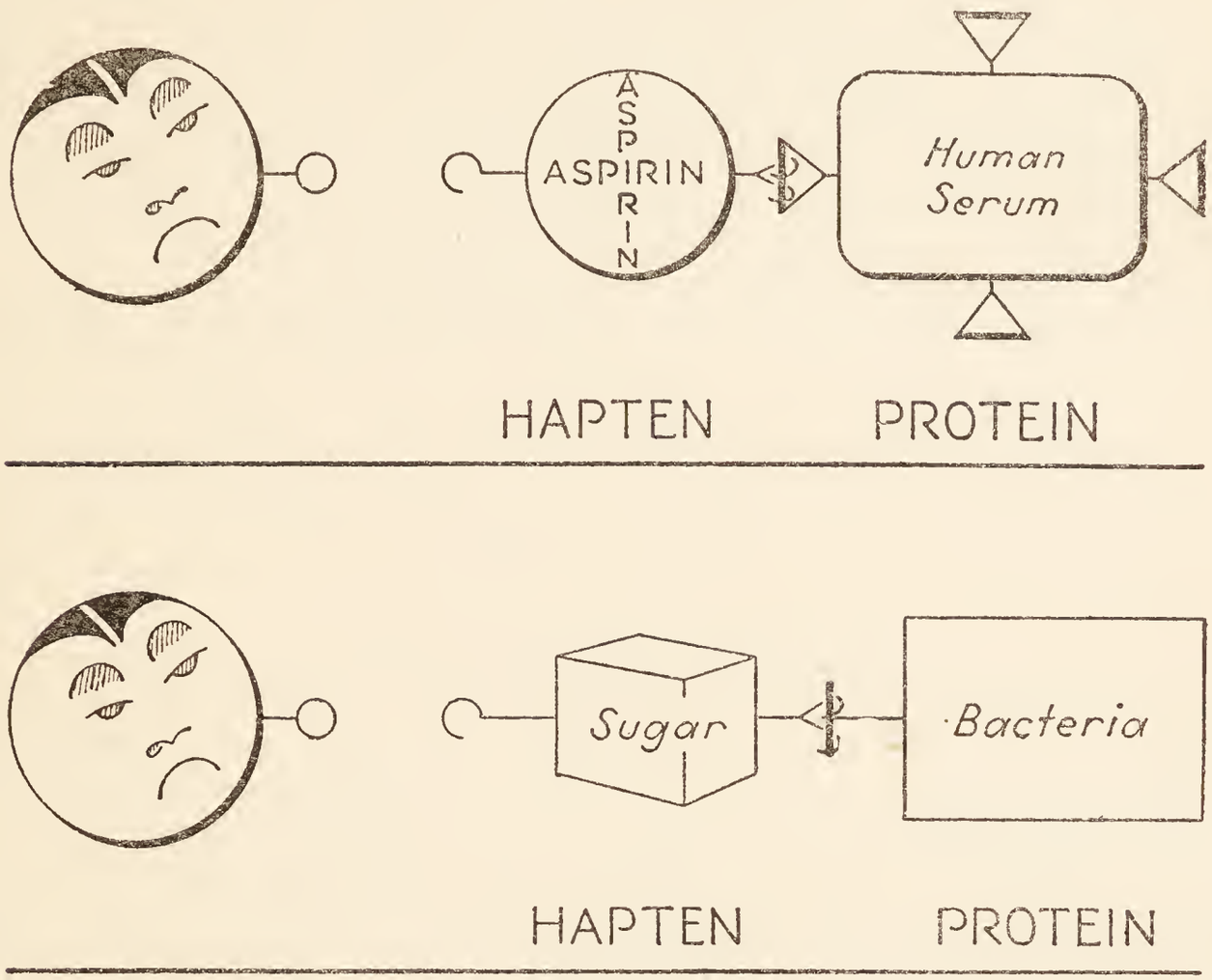

FIG. 21

THE DIFFERENCE BETWEEN DRUG HAPTENS AND BACTERIAL HAPTENS

As we have seen (Fig. 7), a drug which is not protein must combine with some protein in order to become allergenic. The protein-hapten combination represents a new chemical compound which, as far as human cells are concerned, is now a foreign protein.

Hapten action is also necessary in bacterial sensitization, but the bacteria do not combine with human serum to form a new protein. The living cells of the bacteria are themselves protein. In addition to protein these cells also contain certain complex sugars. These sugars constitute the hapten. In the pneumococcus, for example, every different type of pneumococcus has a slightly different sugar. The allergenic specificity of different pneumococci depends on what sugar is present. Type I pneumococcus has the same bacterial protein as Type III pneumococcus, but immunologically, and as far as laboratory reactions and skin reactions are concerned, they are different because they have two different hapten sugars. This is comparable to quinine sensitization being different from aspirin sensitization even though the same human serum is combined with the drug in each instance.

reactive than the scratch test. Much less than a drop was injected. Within sixty seconds the man broke out with hives over the entire skin and developed asthma so severely that ten times the ordinary dose of adrenalin had to be given before he was relieved. Such severe reactions to bacterial vaccines are very rare.

There is abundant evidence that certain forms of arthritis,

rheumatism involving the joints, are associated with sensitization to bacteria, especially the streptococcus.

There is also evidence that bacteria can sensitize only after combination with a hapten. Bacteria do not combine with blood protein to produce a hapten combination as drugs do. Instead they combine with a carbohydrate, a form of sugar, which is built into and becomes a part of the bacterial cellular molecule. In this hapten-protein combination the carbohydrate is the hapten, corresponding to the drug in drug allergy, while the bacterial protein corresponds to human blood protein. This hapten combination has been shown to exist for the pneumococcus, the cause of lobar pneumonia, and possibly exists also for other bacteria.

There are many gaps in our understanding of bacterial allergy.

Chapter XX

DAVID AND GOLIATH

IN OUR REVIEW OF THE INVESTIGATIVE WORK WHICH PRECEDED THE allergic concept we saw that it was the spectacular catastrophe which first caught the attention and stimulated the imagination of the investigator. This was especially the case with diphtheria antitoxin. There was no anaphylactic shock from horse serum until after men commenced injecting this material into people. Had there been no hypodermic syringe, there would have been no serum disease.

Nevertheless in the earlier days, in that era which we may call the period of idiosyncrasy, there were equally fantastic, equally catastrophic episodes caused by the introduction of allergen through the skin.

A farmer was stung by a yellow-jacket bee. The local reaction was the same that you or I would have. When weeks later he was again stung he passed into anaphylactic shock and remained unconscious for nearly two days. A year later he was again stung. He collapsed but revived more rapidly. After several months he was unfortunately stung yet again, this time by two bees. He died within thirty minutes.

A woman was standing on her kitchen porch when stung by a bee. She ran into the house but collapsed before reaching the dining-room. When the doctor arrived she appeared lifeless but slowly recovered after several injections of adrenalin.

Two young sisters were stung at the same time, each by a single bee. Both collapsed in shock. Both recovered after injections of adrenalin.

A man was drinking beer. Too late he realized that he was swallowing a bee. Stung internally, he had severe allergic shock.

These are recent cases, but the experience is not new. There is the record of a farmer who in 1835 was stung upon the temple. He walked to a fence and, supporting himself against it, continued to the house twenty yards away. There he lay down. Ten minutes later he was dead. In 1811 a vigorous man was stung on the nose. With the aid of a friend he walked a few steps to his house. After lying for a few minutes he started to the well for water, stepped a few paces, fell and expired. At about the same time another man, stung on the eyelid, died within twenty minutes.

The first or sensitizing dose is clearly described in the following. In 1927 a woman had about fifteen stings. This was a tremendous dose of allergen, but the reaction was no more severe than normal. When stung a year later she had hives. With subsequent stings she developed asthma. Still later, stings caused shock. Here was a case of increasing intensity of sensitization with repeated injections. She became so highly allergic to bee sting that the handling of an old hat which had not been used for months but which contained many stingers produced an asthmatic attack.

Another victim was so highly sensitized to bee allergen that asthma was brought on by riding in a car with a lap robe which had been used to cover a beehive.

One may be sensitized to bee venom or to the body protein of the insect or to both.

Bites of other insects have caused sensitization. They include fleas, gnats, mosquitoes and bedbugs. One may become sensitized to insect emanations even though there has been no bite. Exposure is through inhalation. The wings of moths and butterflies are covered with small scales and hairs which are continually being shed. These minute particles are in the air in the proper seasons and may be found on the microscope slides used for pollen counting. The emanations from May fly and caddis fly (sand fly) cause considerable seasonal asthma and hay fever, especially around Lake Erie and Lake Ontario.

The common housefly has been incriminated in one instance. A woman had asthma and allergic rhinitis when flies buzzed about her head. Tests with extract of flies' wings were positive.

Sensitization may be treated, usually successfully, with purified extract of the insects or their wings.

It seems probable that many persons are automatically desensitized, the antianaphylactic state being produced by repeated bites. This is seen especially with mosquito bites. Although the sportsmen on vacation in the bayous of Louisiana may complain bitterly of mosquito bites, the native guide living there through the year scarcely bothers to brush the mosquito from his skin, so slight is his reaction. It is said that while explorers in South American

jungles suffer acutely from mosquitoes the Indian guides appear immune to them. They may well have become desensitized by the process of repeated inoculation.

Sensitization to silk should also be considered as a form of insect allergy, reaction being to the dried secretion of the silk moth.

Chapter XXI

A TRULY NEW DISABILITY

IN CHAPTER II WE QUESTIONED WHETHER THERE IS SUCH A THING AS a really new disease or whether all maladies have existed since ancient times. We reviewed the evidence indicating the antiquity of allergic rhinitis. We must now discuss a disease, first described in 1922, which is probably truly new. An added point of interest is that within twelve short years from its recognition the cause had been discovered and its prevention made possible. How different from hay fever, where rational treatment was not devised until nearly a century had elapsed !

In 1922 a German physician, Werner Schultz, described five cases of a previously unidentified disease. As a rule its victims first complained of sore throat and fever. They quickly developed ulcers in the mouth, which spread rapidly. Then followed symptoms of blood poisoning. Death terminated the malady after a week or longer. The astonishing feature of this illness was that the white blood cells, the leucocytes, practically disappeared from the blood. These cells normally circulate along with the red blood cells, the erythrocytes. Their function is protective. They are the policemen of the blood. When germs enter the blood leucocytes engulf and destroy them. When one has a local infection in the skin or elsewhere leucocytes migrate to this area to combat the bacteria and form the chief constituent of pus. Normally each cubic millimetre of blood, each droplet the size of a pinhead, contains from 6,000 to 10,000 leucocytes.

In the disease which Schultz described these pus cells were reduced to 1,000 or less per cubic millimetre. Since a prominent symptom in his cases was sore throat or angina, and since another name for the protective leucocyte is granulocyte, he named the disease *agranulocytic angina*—'sore throat with absence of granulocytes.' He realized that absence of the protective cells and the consequent unmolested spread of germs through the body caused the fatal outcome.

Within seven years 152 cases were recognized. Probably there were many more, not reported in medical journals. Other names have been suggested. Since sore throat is not necessarily a feature

of the disease, *agranulocytosis* was suggested as a more appropriate name. Since the granulocytes are not entirely destroyed but greatly reduced in number, *granulopenia*, or 'scarcity of granulocytes,' was suggested.

The mystery of this disease was solved by three American investigators. In 1933 Dr. Robert Kracke pointed out that it first appeared shortly after synthetic sleeping tablets and aminopyrine, a synthetic chemical substitute for aspirin, became popular. The next year Drs. Madison and Squier proved that the disease is caused by sensitization to aminopyrine. The sleeping tablets and capsules have been exonerated unless they have happened also to contain aminopyrine.

So we have a new allergic disease, different from asthma, hay fever, urticaria, angioneurotic œdema, indigestion and migraine. It appears not to be due to smooth muscle spasm or leakage of fluid from the capillaries. Instead the bone marrow, which manufactures granulocytes, becomes damaged. Most persons can take aminopyrine without untoward effect, but a few who have had it repeatedly react in this abnormal manner. As long as they avoid it the marrow functions normally. Treatment obviously consists in avoiding the drug.

Even now we cannot be certain that this is a new disease. Only within recent years have white blood counts been made routinely in cases of infection. Possibly the disease, existing in previous centuries, was just called malignant angina because no one knew of the changes in the blood. Against this possibility is that additional causes have since been found and in each case it has been a very complicated synthetic chemical compound. These drugs did not exist before Ehrlich inaugurated his researches in chemotherapy.

Although aminopyrine has been widely used, there have been few cases of agranulocytosis. Fortunately sensitization to the drug is rare. Fortunately, also, better remedies have been developed which do not contain the sensitizing chemical radical and aminopyrine is passing out of style.

Other chemicals synthesized for the treatment of this or that disease have occasionally produced granulopenia. Sulphanilamide is an outstanding example. I have described (page 28) the discovery of sulphanilamide as a valuable drug. It was introduced in the U.S.A. in 1937. Even in the first year some cases of sensitization were recognized. Sensitization usually commences between seven and eleven days after the drug is first taken. Once again we find our old familiar incubation period of approximately ten days after the sensitizing dose. Fifteen per cent of those who must take the drug for a long period become sensitized, usually between the seventh and tenth days.

One might question the advisability of using a drug which sensitizes so many persons. But the risk of sensitization is nothing

compared with the danger in allowing the streptococcus infection or pneumonia to continue untreated. With few exceptions, symptoms of sensitization are mild, usually consisting of fever and skin rash, both of which disappear after discontinuance of treatment. Very rarely agranulocytosis occurs.

The blood contains a third solid element besides the red and white cells. This is the platelet. Platelets are necessary for clotting. In allergy to some drugs the platelets tend to disappear, as do the leucocytes in agranulocytosis. When this happens hæmorrhages appear spontaneously under the skin. They look like black-and-blue spots. The disease is called purpura and may be due to causes other than allergy.

Fever is a frequent symptom in drug allergy. At times this creates a problem. Aspirin and sulphanilamide are given to patients with fever to bring the temperature down to normal. Suppose that when the fever is gradually falling toward normal it again rises. Is this new fever due to the infection, in which case the medicine should be continued, or is it due to drug allergy, in which circumstance the drug should be discontinued and another substituted? Fortunately there are usually other symptoms, such as the skin rash, which provide the answer.

With drugs, as with other allergens, the cause may be concealed. A woman with urticaria knew she was allergic to belladonna, but it took many months for her to realize that the cathartic pills which she swallowed each evening contained atropine, a purified belladonna derivative. The man allergic to phenolphthalein, an ingredient of laxatives, did not know that it was used to produce the pink colour of his toothpaste or that it was in the pink frosting of his cake and in his pink ice cream. It is used in many proprietary laxatives and so-called patent medicines, and in only about one-third of these does the name carry any suggestion that phenolphthalein is a constituent. It may be found in preparations advertised for relief of colds, grippe, liver and gall-bladder disturbances and menstrual disorders. Here, as usual, it is a good medicine unless you happen to be allergic to it.

An asthmatic woman who reacted to several allergens was not relieved until ordinary table salt had been substituted for iodized salt. To make certain, she later used iodized salt, with consequent return of asthma. Thereafter she limited herself to plain salt. Another lady, allergic to iodine, could take no laxatives which contained agar. This is a Japanese seaweed with relatively high iodine content.

The most amusing tale of sensitization to drugs is that of the sailor who had a large eagle tattooed on his chest. Cinnabar, a mercury preparation, had been used to make the eyes. Our seafarer later became sensitized to a commonly used mercurial antiseptic. Thereafter whenever he used the antiseptic on cuts or bruises the

eagle's eye became sore and eczematous. Whenever our sailor boy hurt himself his bird would weep, possibly out of sympathy. He solved his problem by changing to iodine for his injuries.

Gland Extracts

The endocrine products constitute a special group of drugs, obtained from glands of different animals. Thyroid extract is the oldest. Although it has caused sensitization, it is less likely to do so than others because it is taken by mouth. Insulin and pituitary extract are injected through the skin. Liver extract may be given either way.

A person allergic to insulin may be reactive to pork, the protein of the animal from which the insulin was obtained. In this case he can change to beef insulin. This internal secretion of the sweetbread, or pancreas, used in the treatment of diabetes, is itself a protein. Consequently one may become sensitized to insulin itself rather than to the animal from which the hormone was obtained. In such cases desensitization is usually successful.

This is usually true of all of the gland products, since sensitization to them more nearly resembles food allergy than drug allergy. With gland extracts we are usually dealing with proteins. In the case of drugs our problem is with haptens. Although successful desensitization against drugs has been reported, it is usually simpler and better to substitute another drug.

Fortunately sensitization to adrenalin, the secretion of the adrenal gland, must be very rare indeed, there having been but a few cases so far reported. I say fortunately because this is the one drug, above all others, upon which doctors must depend for surest and most rapid relief from allergic episodes.

Chapter XXII

FOR APPEARANCE'S SAKE

IVY POISONING HAS BEEN KNOWN IN CHINA FOR MORE THAN TWO thousand years. Two hundred years before Christ the Chinese used crushed crab as a remedy. They still do. The oriental plant, *Rhus vernicifera*, causes lacquer dermatitis, a form of eczema due to handling lacquered oriental goods such as mahjong sets, walking sticks and the like. Orientals wear gloves when handling fresh lacquer and, even so, many of them develop dermatitis. After the lacquer has dried and become oxidized it is only feebly allergic. Consequently few persons in this country have trouble from handling oriental products.

The New World variety of ivy poisoning was part of the unfor-

tunate experiences of the early explorers. Captain John Smith described the plant as being in shape but little different from English ivy but causing redness, itching and blisters. "*It hath gotten itselfe an ill name, although questionlesse of noe very ill nature.*" The Spanish Conquistadores had their share of trouble. An expedition into what is now New Mexico suffered seriously in 1719.

Neither the oriental sumac nor American poison ivy or poison oak is found in Europe. Europeans are, however, not altogether fortunate, since they experience similar trouble from primrose.

Ivy dermatitis fulfils the requisites for classification as an allergic phenomenon. Persons who have never been exposed to ivy do not react to it. They do not react on first exposure. An incubation period of ten days after the first contact is required before dermatitis can be produced. If skin from a person with contact dermatitis be transplanted on to the skin of one not so sensitized and, after healing, patch tests are done (a) on the transplanted skin and (b) on the second person's own skin, only the transplant will react.

Other Causes of Contact Dermatitis

Many plants besides poison ivy, poison oak, poison sumac and primrose will cause sensitization, although less easily. For some unknown reason the four mentioned are more potent sensitizers than other plants. Ragweeds and the grasses may cause contact dermatitis as well as inhalent allergy. Here it is a matter of brushing against the plant. The farmer who has eczema of the face, hands and ankles at the same season each year is probably allergic to the oil or juice of some plant. The allergen is different from that which causes inhalant reactions. The latter may be extracted from pollen in watery solution, while the former must be extracted in oil.

A Texas physician tested patients who had contact dermatitis with fifty-one different plants, not including poison ivy. Cocklebur, corn, fennel, aster, gaillardia, snow-on-the-mountain, trumpet vine, sunflower, cotton and privet are a few of them. Twenty-four plants gave positive reactions on one patient or another.

Florists often have dermatitis of the hands. It is so common among those who handle tulip bulbs that the condition is called 'tulip fingers.' In contrast to the high sensitizing capacity of ivy, with sensitization possible after a single exposure, other plants usually require prolonged and repeated exposures.

Sawdust dermatitis is not unusual and is caused by such diverse woods as satinwood, oak, ebony, teakwood, Japanese hardwood, rosewood, mahogany and birch. Sensitization to one is usually specific and does not imply sensitization to the others. The list is quite like that of sawdusts which cause asthma. They may cause either reaction but not necessarily both.

Paper sensitization is, in the last analysis, sensitization to a plant

product. A postman has dermatitis of the hands and legs from newspaper. During the week he has a stuffy nose and sneezes when distributing the papers at the post office. The larger Sunday papers produce much heavier exposure. He has eczema regularly on Sunday evening and Monday. Local eczema from sanitary napkins may be classed as plant dermatitis.

Some smokers have eczema of the lips due to tobacco.

Animal products may cause trouble. The commoner are feathers, furs, wool, clothing and leather. Drugs, chemicals, cosmetics and soaps cause much difficulty. Occupational or industrial dermatitis is often associated with sensitization to some substance handled in routine work.

A dentist was allergic to novocain, developing eczema of the hands after each tooth extraction. This is not uncommon. He wore rubber gloves, using every precaution to avoid handling novocain, but continued with his attacks of eczema. Patch tests showed sensitization to the latex rubber gloves. He was then tested with several brands of gloves. He was negative to one of the older types of composition rubber. After changing the brand of gloves he ceased having trouble.

Girdle dermatitis is uncommon. It is usually due to the rubber in the girdle. Dress-shield dermatitis is quite common. It may be caused by the material of the shield but is more often due to the chemicals added to give the shields a pretty sheen when new. In this case the lady who has trouble whenever she buys new dress shields need but wash them thoroughly before wearing them.

The three cases which follow might very well have been mistaken for sensitization to human beings. A man had itching of the genitalia, usually coming on about four o'clock in the morning. He was allergic to rubber. Another with the same complaint had suffered with eczema of the scalp, traced to a hair tonic containing quinine. The new symptom was traced to a contraceptive suppository which also contained quinine. Shortly after his honeymoon a man in his early thirties developed eczema of the lower half of the body. He had never had it before. When away on business he improved, but after one night at home the condition became as bad as ever. He reacted to silk. His bride discarded her silk nightgowns. Within two weeks he was a well man. She wore silk again, and overnight the eczema returned. Cotton was *de rigeur* thereafter.

These are not cases of allergy to individuals, yet they are due to contact with another person. More properly they should be described as allergy associated with cohabitation. The cause in such cases may be most difficult to trace. An example was the young married man with dermatitis due to his wife's perfume. This was not the same man, mentioned previously, whose fiancée's perfume caused sneezing and wheezing.

Occupational dermatitis is not confined to factory workers. A business man had a ring of eczema around his mouth, involving the lip, cheeks and chin and so definitely circular in distribution that the doctor had a good lead as to the size and shape of the excitant. Patch testing confirmed his suspicion of the plastic mouthpiece of a dictating machine.

This same man had dermatitis around his ankles, caused by shoe polish. Thus we see that in contact dermatitis, as in other forms of allergy, one may be sensitized to more than one substance. Indeed, it has been found that persons with an eczematous tendency are more likely to become sensitized to new contact factors than are those who have never had this tendency.

The housewife, the secretary, the cook and the maid are no freer from the hazard of occupational dermatitis than is the stableman, the printer or the millworker. The eruption on the cook's hand may be from handling certain foods or it may be from soap. The maid's trouble may be from flea powder used on the dog, furniture polish, clothes sprays or other moth preventives. A secretary had eczema of the finger tips which looked like 'tulip fingers' although she never handled tulips. The cause was traced to the carbon paper in her typewriter. Patch tests showed that a different brand was harmless. The housewife doing her own housework may become sensitized to any of a hundred or more things regularly used at home.

A little girl had eczema of the buttocks. She reacted to soap. All that was needed to effect a cure was for her mother to rinse the panties more thoroughly after washing. Persons allergic to soap do not usually react to all varieties. Testing will show that some may be used safely.

One may become sensitized to ointments prescribed for the treatment of skin affections. This is seen especially in scabies, 'the itch.' The victim is so upset with the knowledge that he has this undesirable affliction that he continues to apply the ointment after he has recovered, hoping to prevent any future reinfection. After a time skin lesions appear again. He is certain that he has another attack of scabies. The truth is that he has become sensitized to the ointment. Others become sensitized to the ointment used to cure trichophytosis, 'athlete's foot.' One gets the lesion nearly clear. Then it returns. Believing that he has reinfected himself, the victim anoints himself more lavishly and his eczema becomes worse.

Contact allergy may affect mucous membranes as well as the skin. Stomatitis, irritation in the mouth, may be due to artificial dentures or to the material used to make the plates stick to the palate. Fortunately there are many kinds of material from which plates may be made, so that one can usually find a safe substitute.

The victim of denture stomatitis will usually give positive skin reactions to the offending substance. The skin and the mucous

membrane react. The reverse is not always true. A substance which causes eczema may produce little or no reaction in the mucous membranes. Poison ivy taken internally in small doses usually does not irritate the mouth or stomach. It may, however, irritate the skin after having passed through the entire length of the intestinal tract, as we may see from the following, written a hundred-odd years ago.

"Some good-meaning, mystical, marvellous physician, or favoured ladies with knowledge inherent, say the bane will prove the best antidote, and hence advise the forbidden leaves to be eaten, both as a preventive and cure to the external disease. I have known the experiment tried, which resulted in an eruption, swelling, redness and intolerable itching around the verge of the anus."

Cosmetics

Five thousand years before Christ Queen Shub-ad of Ur painted her nails and plucked her eyebrows. Three thousand years ago in Egypt Queen Nefertiti painted her finger and toe nails red. The ancient Egyptians, Greeks and Romans knew nearly all the tricks of beautification that we use to-day. Their chemicals were different —vegetable dyes, malachite, ochre, galena, frankincense, myrrh, chalk—but the principles were the same. From the day of the earliest savage, man or woman has painted the face and body. Cosmetic dermatitis probably existed in all ages although there is equal probability that it is more common now, due in part to more widespread use and in part to the synthetic chemicals and aniline dyes which, like poison ivy, appear to have greater sensitizing capacity. Orris root is not the only constituent of cosmetics of which allergic ladies must be wary. One may react to the dyes of lipstick and rouge, to rice powder or other constituents of face powders, to cold creams and vanishing creams, nail polish, hair dyes and to the ingredients of eyebrow pencils and various other substances for beautifying the eyes. A woman had diarrhœa which was traced to sensitization to her lipstick.

Evidence suggests that allergy is increasing with the increasing artificiality of our environment. The newer synthetic chemical drugs are more potent in the treatment of disease, but they are more likely to cause allergy than the more natural drugs from the plant kingdom. Chemicals used in industry, which did not exist until the ingenuity of man created them, often appear to be more highly allergic than those which have been with us through the ages. The newer dyes in cosmetics probably cause more trouble than did the simple vegetable colourings of previous ages. As the world becomes more complex the problems of allergy become correspondingly more complicated.

PART FIVE

MAN AND HIS ALLERGY

Chapter XXIII

A NERVOUS DISEASE, AFTER ALL?

SHE WAS AN ATTRACTIVE GIRL WHOSE BEAUTY WOULD JUSTIFY A covert second glance as she passed. But she had hives. She had been tested repeatedly with food and inhalant allergens, and the possibility of drug sensitization had been ruled out. There were no concealed allergens. In short, this girl had an allergic symptom but no recognizable allergy.

The cause was uncovered only after repeated painstaking explorations of her daily routine, her associations and her problems. It was nothing that she had ever associated in her own mind with her skin eruption. There was no reason why she should.

A certain young man had monopolized her time. He was a possessive fellow. When his attentions became too ardent she felt that it was time to terminate the affair. This would have been quite all right had he been amenable, but he refused to accept his dismissal. Soon he became a bore, then a pest. Finally he was downright objectionable. Pleading and cajoling having failed, he tried unpleasant threats. It was at about this stage that her urticaria commenced.

She had discussed her problem with no one and, because she saw no possible connection, she had not mentioned it to the doctor. It was not until her physician, realizing that emotional factors might be of importance, questioned her that she spoke of her problem. On his advice she sent the young man his final dismissal in a letter. Within a week, when it appeared that he had accepted her decision, her hives faded away.

Three months later she was again at the doctor's office. The hopeful swain had returned to the attack. His advances had become so distasteful that the doctor and his patient consulted the judge of the juvenile court. The latter directed a police officer to notify the young man that his persistence would speedily result in a court experience. He at last desisted. In the ensuing nine years the

young lady, who is now happily married to another man, has had no return of urticaria.

A man in his middle fifties also complained of urticaria. He reacted to house dust, was given a series of injections with this allergen and was well after a few weeks. Eight months later hives returned. After another course of dust injections he was again relieved. The doctor saw nothing of him for a year, when he had yet another episode of urticaria which once again appeared to respond to treatment. Naturally the doctor believed that the dust injections had turned the trick. It was not until some time later that he learned the incorrectness of his conclusions.

The man had married a young girl. He was devoted to her and had every reason to believe that she felt likewise towards himself. His first attack came on after he discovered that another man shared her affection. It wasn't the dust injections that relieved his hives. Either he adjusted himself to the situation or more probably believed that she had terminated the affair. The second attack was caused by her announcement that she was leaving to procure a divorce. Once again, after a period of emotional readjustment, urticaria disappeared. The third and final attack followed receipt of a letter from his now divorced wife, asking him to send her bedroom furniture.

A New Kind of Allergic Excitant

What new element is this which must be fitted into the crazy pattern of the allergic picture? First we learn that allergy is a matter of protein sensitization. Then we discover that drugs which are not proteins may cause the disease. Next, an almost unlimited assortment of non-protein substances can produce allergy of the skin even though they do not penetrate the body. Finally, heat, cold, sunlight and mechanical irritation may do likewise. Scientists have rationalized each of these discoveries in turn, providing intelligible explanations and showing how these several forms of allergy are interrelated in spite of their apparent diversity. Must we now also speak of mental or emotional allergy? Certainly no protein or hapten plays a part. Although heat or sunlight might injure abnormally reactive tissues to such an extent as to liberate histamine, surely one would not suggest that thought processes, even those associated with emotional tension, will do likewise. Would it not be better to say that urticaria may be caused either by allergy or by nervous factors?

Here then is our problem. Are we still discussing allergy or are we now viewing a different disease? Certain philosophic considerations make the theory of an integration of the emotional response with other allergic responses most attractive.

Allergy implies an altered or abnormal reaction. Certainly the young lady and the married man reacted to their emotional prob-

lems in an abnormal way. Using this broadest possible concept of the term, their reactions were allergic. There are, however, dangerous pitfalls to this broadest possible concept. I stub my toe and don't say damn ! My reaction is abnormal. So I am allergic to stubbing my toe. A deaf person doesn't jump when a firecracker explodes. He should have. Deafness, then, is an allergic disease. No, we must safeguard our definition. The allergic person reacts in an abnormal way, but this abnormal reaction follows a pattern. It takes the form of hives, asthma, allergic rhinitis, headache, colitis, one of the specific physiologic alterations with which we are now quite familiar. The manner of the altered reaction must now be included in the explanatory definition.

If certain persons react emotionally, with resultant allergic symptoms, we should try to find some relationship to allergy. This is the same rationalization used years ago in making drug idiosyncrasy into an allergic disease. Similar theorizing eventually provided an adequate explanation for physical allergy. In drug allergy and physical allergy the idea that allergy plays a part was first suggested because of the similarity in symptoms. The same applies in the emotional responses of our girl and man. Their symptoms are allergic, their reactions are altered. Is there a logical explanation for this apparent similarity ?

Emotional Influences

Before delving farther into this problem let us improve our orientation to it by means of additional case experiences.

A young lady in her twenties had hives which always disappeared when she left home. She reacted to several foods and inhalant allergens, but their avoidance gave no relief. Her aunt, an otherwise fine woman and an unusual business executive, was addicted to alcohol, often to excess. She lived with her aunt and was devoted to her. She spent most of her time protecting her and trying to persuade her to forego her drinking. At the same time she was in love with a young man whose income was sufficient to provide ample comfort for a family. He was constantly importuning her to marry him, but she believed it her duty to stay with and protect her aunt. When at last the doctor persuaded her to marry the boy her disease disappeared.

A banker had urticaria and angioneurotic edema from tomatoes. He solved his problem by not eating them. But during the bank holiday of the depression he had a business problem which could not be solved so easily. His hives returned. No specific cause could be discovered. When the acute financial stringency of the depression was over, so also was his urticaria.

A young business woman, a buyer for a clothing firm, ate shrimps and chocolate while in New York. She knew she had been allergic to both but had found during recent years that they no

longer caused trouble. Returning to the hotel, she received word that her mother had been in an automobile accident. She promptly had hives. Taking the first train, she reached her mother's bedside to find the injury slight and that there was no cause for alarm. Though her mother left the hospital the following day, urticaria continued. Some weeks later she consulted a physician, who found her allergic to shrimps, chocolate and strawberry. She avoided them but still had no relief. She was then found allergic to coca-cola which she drank each day. When she omitted this also, her urticaria at last disappeared.

In the analysis of these cases three facts stand out rather prominently. First, they all had urticaria. Unless some special shock tissue is predisposed one would anticipate this more generalized reaction to emotional factors. We shall see, however, that local shock tissues may also be involved. Second, all but the first had some other allergic sensitization, usually to foods and inhalants. In the majority, therefore, we are dealing with the same people who have the more conventional type of allergy. Third, the last case suggests that a conventionally allergic person who has become so adjusted to food allergens that they no longer cause trouble can experience such an upset of this state of equilibrium, consequent on emotional disturbances, that previously harmless foods now cause symptoms.

This last is also brought out in the two cases which follow. A man with sick headaches due to wheat found that he could eat bread once a day with safety. Following an emotional upset his headaches returned. These were not relieved until he completely discontinued eating all wheat products. His tolerance to an allergenic food had been diminished by an emotional episode. A woman with hay fever was receiving perennial treatment, with injections of pollen extract twice monthly, the dose being always the same. She had had no trouble from any of the injections. Shortly before a treatment she had an emotional upset. That injection, the same amount as usual, caused hay fever and anaphylactic shock. After recovery from this she no longer tolerated as large a dose of the extract as formerly.

These were two cases in which local shock tissues (brain and nose) were especially predisposed. Subsequent symptoms were referable to these tissues rather than appearing as urticaria.

A childless married woman sneezed and had hives whenever she saw her sister's baby. It developed that her unmarried sister, who had become pregnant, had lived with her and her husband until the baby was born. They adopted the baby, becoming devoted to it. A few years later the baby's mother and father were married and claimed the child. The foster parents refused to give him up. During the unpleasant episodes which followed, the foster-mother commenced having hay fever and hives. Finally, to prevent a

legal battle, the child was relinquished. Since that time whenever the elder sister visits the youngster's home or when he comes to her home she has paroxysms of sneezing with urticaria. As long as she does not see the child she remains well.

A young student cannot eat eggs or tomatoes without developing angioneurotic edema or other allergic symptoms. When studying for examinations he has his attacks of swelling even though he has not eaten eggs or tomatoes.

An asthmatic woman was in an automobile accident. Her husband was driving. Thereafter whenever he would apply the brakes suddenly, or when she thought that he should do so, she would wheeze.

A lady with chronic asthma, adequately controlled, mentioned to her doctor that her cough medicine was not of the usual colour. For this reason she had not used it. He tasted it, agreed that something was wrong and took it to the druggist. The druggist also tasted it. While the doctor was with the druggist the lady discovered that someone had put hair tonic in the bottle. Imagining that the doctor and the druggist were poisoned, she promptly had severe asthma. This persisted until she was convinced that they were in no danger.

An asthmatic girl was very much in love with a lawyer. He knew nothing of this nor was he particularly interested in her. She found it difficult to control her emotions when with him but did so successfully. The mental turmoil always ended in an attack of colitis. In short, whenever she was with the object of her desire she had an attack of diarrhœa. Those who are not allergy-minded would speak of this merely as a case of nervous indigestion. But note that here, as with the others, there was other evidence of allergy.

Disordered Protection against Harmful Environmental Factors

We speak of the trigger mechanism. An asthmatic attack might be looked upon as an explosive response to stimulation by the specific allergen. The tendency to have asthma must be present. One must first be allergic. The more frequently allergens cause explosions of asthma, the more often they set off the trigger, and the easier it will be for other non-specific factors also to pull the trigger which initiates attacks. After a man has had many attacks of asthma due, let us say, to feathers, he will eventually get into the asthmatic habit and may thereafter have attacks caused by other non-allergic factors. These may be such as fatigue, infection, constipation, mechanical irritation, climate, endocrine disturbances and emotional upset.

Because the emotional responses that we have been discussing appear in the form of the common allergic symptoms and usually occur in persons who are otherwise allergic, it is desirable to rationalize the picture in terms of allergy.

To do this we must return to certain fundamental considerations Remember that Ehrlich explained allergy chemically as an altered immunity reaction. Immunity means protection. When one is immunized one is protected. It is a point of utmost interest that the shock tissues active in allergy are primarily protective tissues. Their normal function is that of guarding the body against harmful outside agents. If one gets something harmful in the nose, whether it be a fly, road dust or an irritating gas, the protective mechanism in the nose causes sneezing and an increased secretion to wash away the harmful substance. Should a similar substance get into the trachea, the circular bronchial muscles contract in order to keep it from getting farther down into the lungs. At the same time one coughs in an effort to expel it. But this sounds like the symptoms of hay fever and asthma ! The stomach protects through the vomiting reflex or, if this fails, the intestines pass the harmful substance on as rapidly as possible, with consequent diarrhœa, a symptom of colitis. If one burns the skin, a blister forms. This is an accumulation of fluid to protect the tissues deeper in. In urticaria there is a similar accumulation in the deeper skin tissues, primarily protective in function. Since it is deep no actual blistering occurs. In the swelling of angioneurotic edema the reaction is still deeper, well beneath the skin, but we can conceive of its function as that of bathing the cells in protective fluid. No one knows the true pathology of migraine or sick headache, but recent observations indicate that it may be a local angioneurotic edema. In chronic irritation of the skin there is weeping, as in weeping eczema, a leakage of fluid through the skin in an effort to wash the harmful substance away. The smooth muscle of the uterus contracts primarily for the purpose of removing a foreign body from this organ.

Speaking now in terms of human physiology rather than of chemistry, the allergic reaction is primarily a protective response which for some reason is not co-ordinated. It represents a failure of satisfactory adjustment to deleterious influences which arrive from outside. The reaction is purposeful but it is purposelessly executed.

One cannot but be intrigued by the realization that those persons with allergic symptoms caused by emotional upsets, as described in this chapter, have also been unable satisfactorily to adjust themselves to certain problems. Although they have been mental problems, they have represented deleterious environmental influences.

In emotional allergy, as in ordinary allergy, we are dealing with failure of satisfactory protective adjustment.

Chapter XXIV

ON SELF-PROTECTION

I HAVE SAID MUCH CONCERNING THE CHEMICAL CHANGES DURING THE allergic reaction and those physiologic responses, smooth muscle spasm, capillary hyperpermeability, etc., that take place in the shock tissues. We must give some attention to certain changes in the nervous system, that regulating organ which in allergy appears to have lost its ability to govern. We must make the acquaintance of the autonomic nervous system. This is the system of nerves of whose existence we remain quite unconscious as long as it functions properly. It is not the nerves with which we feel pain, heat or cold, or the nerves of the special senses through which we become conscious of seeing, smelling, and hearing. It is not the nerves whose activity we voluntarily control when we talk or swallow or direct our muscles to move us about. It is a system of nerves which automatically controls the functions of the organs and tissues within our bodies. It is because of autonomic (automatic) activity that the pupil dilates and contracts, that the lachrymal glands secrete tears, that the glands in our mouths secrete the proper amount of saliva, that digestion proceeds in a normal manner, and that the muscles of the blood vessels always remain in the proper state of contraction or relaxation. This system of nerves controls the rapidity of the heartbeat and influences the function of practically all of those structures within our bodies which are connected with the nervous system.

Our present interest in the autonomic system is that it controls the activity of smooth muscles, those muscles which become too active during the allergic reaction. This control is maintained by two divisions or sets of these nerves which act antagonistically toward each other—one might say in opposite directions. One set, the *sympathetic*, causes relaxation of certain muscles, while the other, the *parasympathetic*, causes their contraction. The actual state of tonicity of the muscles depends upon relative preponderance of action of the two nerves. The allergic shock tissues are controlled by these two opposed groups of nerves. Under normal conditions, in a state of inactivity, the two sets are equally active and the muscle is at rest, neither highly contracted nor abnormally relaxed. Under conditions of physiologic activity one nerve system or the other becomes dominant.

What will happen when the sympathetic set becomes dominant?

I shall get a little ahead of my story and tell you that it is the sympathetic system which in great measure controls our adjustment to our environment. It controls the protective reactions. As long

as it has the upper hand we need have no fear of allergic responses. It is when the parasympathetic gets control that we experience difficulty in adjusting ourselves to environmental influences.

Sympathetic Nerves

Returning to the question of what happens when the sympathetics are stimulated, let us take a very general problem of adjustment to one's environment. A bully starts teasing his schoolmate. Here is really a problem. The victim must either fight or run. His sympathetics go into action. Watch closely to see how everything that this automatic nervous system does will make it easier for the boy either to fight or run, to adjust himself in one way or the other to his problem. The boy breathes faster and more deeply. His bronchial muscles have dilated and he is getting more air into his lungs. More oxygen will be transported by the blood from the lungs to the muscle cells, which will need it badly if they become very active. His heart beats more rapidly. This helps because it carries the blood around its circuit in shorter time, facilitating rapid delivery of the oxygen. Under the nerve stimulation more red cells are poured into the circulating blood so that more oxygen can be carried by them to the tissues. There is a redistribution of the blood, less of it going to the inner organs and more being shunted into the muscles. He will need more fuel to burn, to keep up his muscular activity. The sympathetic system stimulates the liver to release stored glycogen into the blood. As it is released the glycogen is transformed into sugar, the energy food, and the level of sugar in the blood rises. The sweat glands become more active, thus providing for rapid loss of heat. At this stage the blood will clot more rapidly than normal, thus providing protection in case of injury. Truly, the boy is ready now for either combat or flight.

What would happen if the sympathetic system were so damaged that it could no longer provide these facilities for adaptation to sudden need? Scientists know the answer because they have been able to render the sympathetic system completely inactive. Dr. Walter Cannon has found that under these conditions an animal will live without difficulty unless subjected to stress. A cat will live as a cat should, but bring a dog into the room and its fur no longer stands on end. Nor do those other changes which we have just discussed occur, changes which are so necessary for its protection against dogs. The cat must be kept at an even temperature, since it has lost its ability to protect itself against change of temperature. Once a warm-blooded animal, it has become cold-blooded.

Adaptation to environmental problems may fail because of under-activity of the sympathetic system or because of over-activity of the parasympathetic. This latter is what appears to happen in allergy.

The Fight-or-Run Hormone

A unique feature of the sympathetic system is that it is connected directly with the adrenal glands, those little organs which manufacture adrenalin and deliver it directly into the blood. These glands are really a part of the sympathetic system. Under normal conditions the adrenals are inactive, and the sympathetic nerves control the activities of muscles and glands and other body functions through their direct nerve connections. The adrenals are, in a measure, storehouses for adrenalin, for use in emergency only. Normally they secrete very little adrenalin into the blood. But when our little boy was threatened by the bully the adrenals at once became active, pouring large quantities of adrenalin into the blood to be distributed through the body. The process might be compared to the second alarm of a two-alarm fire. The body must have some emergency system ready at all times to take care of an unusual situation, and this is the way it is done. Adrenalin stimulates the cells to respond in the same way that they do for the sympathetic nerves, but the stimulation is many times more intense. It is the difference between clucking at a plodding horse and cracking a whip. When you get mad and 'see red,' as the saying goes, your adrenal glands have flooded the blood with adrenalin. When the fight is over and you stand trembling do not interpret it as fear. Although the need has passed, the adrenalin is still stimulating the tissues to such activity that they cannot remain quiet, and you tremble as a result.

The Parasympathetic Nerves

What about activity of the parasympathetics? In general, the effect of their stimulation is the reverse of sympathetic stimulation. Bronchial muscles contract instead of dilating to permit more air to enter. Certain blood vessels dilate and the capillaries allow fluid to pass out because they have become increasingly permeable. Stimulation of the parasympathetics causes the secretion of acetylcholine. This is a hormone comparable to adrenalin, but it is not secreted in such large amounts. In contrast with adrenalin, it is rapidly destroyed in the blood. As a consequence, it exerts its effect only in the neighbourhood of the stimulation. There are certain regions where it seems to be especially abundant after stimulation, and these are our old familiar allergic shock tissues. If there is over-activity of the parasympathetic system in the bronchi, acetylcholine is produced locally, the bronchial muscle goes into spasm, and asthma results. Similar processes may occur in other shock tissues. It is only in generalized anaphylactic shock that such an excess of acetylcholine is produced that it may be found in the blood. Then it may be carried to all parts of the body. This explains the severity of shock.

The autonomic system adjusts us to our environment. Normal adjustments are made by preponderant activity of the sympathetic portion of the autonomic system. If for some reason the parasympathetic portion is over-active, maladjustment ensues, and the individual is unable adequately to cope with external environmental forces. For some unknown reason, in the allergic reaction there appears to be local preponderance of parasympathetic activity.

How shall this be overcome ? We must stimulate the sympathetic system, of course. Fortunately, adrenalin is available as a drug for injection. We inject it under the skin and it is rapidly absorbed into the blood. Since, unlike acetylcholine it is not destroyed in the blood it is carried to all shock tissues and relieves the allergic symptom, no matter which tissue is involved.

If we could make the patient 'see red' each time he had an allergic attack, he might not need adrenalin injections. This has happened on rare occasions. An asthmatic man found that whenever he gets excited or angry during an attack of asthma the latter is relieved. It is said that William of Orange, a chronic asthmatic, was always relieved when in the heat of battle. Macaulay, after describing William's constitutional asthma, wrote, 'One of the most remarkable peculiarities of this man, ordinarily so saturnine and reserved, was that danger acted on him like wine, opened his heart, loosened his tongue, and took away all appearance of constraint from his manner.'

The Whole Story

And so you have the story. Antigen combines with fixed antibody, damaging the tissue cells. This releases histamine. Histamine stimulates the parasympathetic system to secrete acetylcholine. This in turn over-stimulates the parasympathetic system. The parasympathetics then cause muscles to contract or dilate, depending on their location, increase the permeability of capillaries, and cause various other responses. The result is the allergic reaction. We are not yet certain whether the histamine causes the secretion of acetylcholine or *vice versa*, but this is a minor point which will be worked out in time. Our understanding of the working of the autonomic system will, like the explanations of allergy, be modified as our knowledge broadens.

Chapter XXV

ON THE RINGING OF A BELL

THE NERVOUS SYSTEM PARTICIPATES IN THE ALLERGIC REACTION through the activity of its autonomic nerves. Furthermore, there is evidence of nerve participation even though the reaction be

purely local and due to allergens, as in pollen hay fever or local angioneurotic œdema or urticaria caused by foods.

If a man with physical allergy (one who has hives when he is exposed to cold) has an elastic band placed around his right arm so as to completely stop the circulation and then dips the right hand into cold water, he will break out with hives. The important fact is that he has hives not only up the arm as far as the elastic band but also beyond the band and in other parts of the body. Histamine could not have been carried to these remote parts in the blood because the blood is not circulating below the band. The only way in which remote areas could have been stimulated would be by way of the nerves. If a portion of this man's skin be anæsthetized so that the nerves to that area are thrown out of commission, he will develop hives elsewhere but not in the anæsthetized area.

Now let us recall our discussion of the trigger mechanism (page 132). When a shock tissue has developed the habit of responding to stimulation by an allergen the trigger mechanism is set, and non-allergenic stimulation may set it off. A person whose hay fever is due to house dust and whose trigger mechanism is set may sneeze from the irritation of ordinary road dust, from looking at the bright sun, from infection in the sinuses and even from emotional upsets. The autonomic nervous system is connected directly with the brain, and the trigger may be released by nerve impulses as well as by external irritants. Indeed, the person who sneezes when looking at the sun could do so only because of transmission of the stimulus from the eye to the nose by way of the nerves.

Shall We Hurl Rolling Pins?

As far as the autonomic system is concerned, there are two types of people, the adren-ergic and the cholin-ergic. The adren-ergic are those who secrete large amounts of adrenalin into the blood when they become excited. Their sympathetic systems are more active than the parasympathetics. They get mad and throw dishes. They are not the people who develop allergic symptoms. They adjust themselves explosively to environmental problems and have no further trouble.

The cholin-ergic crowd are controlled by their acetylcholine, by preponderant activity of the parasympathetic system. They don't throw flat-irons. They are reticent. They keep their problems to themselves. They do not 'see red.' Instead they break out with a crop of hives or have sick headaches. Their adjustment to environmental problems may be better as far as the artificialities of modern life are concerned, but they are poor when measured by the yardstick of primitive hot-blooded man. Since we are not yet too far removed from the cave man we may with justice still look upon the combative reaction as normal and upon the repressive response

as an abnormality necessitated by the exigencies of modern existence.

All the instances of emotional allergy which I have described have been in persons with strong emotional reserve. When the doctor finally worms it out of them and helps them to see their problem from an impersonal point of view and suggests appropriate measures for solving their difficulties their allergic symptoms improve or disappear.

The factor of reserve is well illustrated in the poker player with the so-called poker face. All went well as long as he was winning. When he was losing there was no change in his facial expression. The only difference was that he would scratch here and there. He had hives.

A lady had intermittent swellings of the lip, when it would become three times its normal size. Allergic studies showed that three or four foods would cause this reaction. Whenever she had an unpleasant argument with her husband the lip would swell as much as after eating eggs. She never told her friends about the arguments. She just said she had eaten an egg.

The Conditioned Reflex

Even the conditioned reflex may release the trigger. 'Conditioned reflex' sounds quite formidable. It is really quite a simple term coined by the great Russian physiologist, Pavlov, to describe an interesting sequence of physiologic events. Pavlov experimented on animals in which he could study the secretion of the digestive juices. The set-up was somewhat as follows. Show a hungry dog a nice meaty bone. Don't give it to him, just show it to him. This makes him still hungrier. The stomach at once starts secreting digestive juice, getting ready to work on the bone. It makes no difference whether or not you give the bone to the dog at that time. The digestive organs get ready for it in either event.

Next, ring a bell every time you show the bone to the dog. Don't ring it at any other time. After many repetitions the dog subconsciously connects the ringing of the bell with the idea of food.

Finally, just ring the bell. The digestive organs will start working just as promptly as though the dog had seen a bone. The secretion of stomach juices under the stimulus of the bell is conditioned on the dog's mental association of the two ideas. The bell means food.

We should note that it is purely a reflex response, not dependent on conscious interpretation of the significance of the bell.

Many are the experiences of our everyday life in which the conditioned reflex plays a part. I have a small fishpond. I feed the fish always from the near corner of the pool. Since they are usually hungry they come scurrying when I drop the bits of food

on the water. For many weeks I have clapped my hands vigorously when feeding them. To-day I can stand at the far corner of the pool, clapping my hands. The fish have learned to associate the noise with the idea of food, and to come swimming toward me. To-day they swim away from me instead. It isn't because they know that this time I have no food and are angry. It is because I have changed my position to the far corner and they have come to associate the clapping of hands and the other corner of the pool with the idea of food.

A lady was so strongly sensitized to watermelon that she couldn't even keep it in her stomach. She had had the experience so often that melons had become most distasteful. She might be enjoying a delicious meal in a restaurant. If a stranger at a nearby table had watermelon and she chanced to see it, she would vomit. Thus the conditioned reflex enters even the problems of allergy.

In one clinic, where many men and women were receiving daily pollen injections, the doctor posted the pollen counts each day so that his patients could know what was happening in the air. When the counts were low their symptoms should be better. When high they might have trouble. The doctor was interested in the power of suggestion on the appearance of allergic symptoms. One day, when the count was lower than usual, he falsified the curve to show a high increase in pollen concentration. The patients were doing nicely, and should have continued so, but before the day was out three of the many who had seen the curve were having severe hay fever !

Many years ago, when the idea of allergy was new and scoffers were numerous, a doctor persuaded a lady who knew that her asthma was caused by roses to sniff at a rose. She had the customary response, an asthmatic seizure. Then he unkindly informed her that it was an artificial rose. This case has often been cited in support of the contention that allergy is an imaginary trouble, but the artificial rose was as clear an example of the conditioned reflex for the lady as was the ringing of a bell for the dog.

The conditioned reflex may act in reverse, as it were. A person with asthma may become worse and more resistant to treatment as a result of apprehension concerning his condition. Such a patient is often relieved with sedatives or after being given a mild anæsthetic; something to relax the nervous tension and to break the vicious circle.

The reverse may be seen in asthmatics or other victims of allergy who improve for a time after taking this or that patent medicine or secret formula, which, they have been assured, will bring relief. The advertising matter accompanying such nostrums has conditioned them for improvement and, anxiety having been relieved, they improve even though there may be nothing in the medicine that should help in any way. Unfortunately, the mental factor is

FIG. 22

THE VICIOUS CIRCLE OF ALLERGY

Vicious circles are seen in allergic reactions because various excitants, both allergic and non-allergic, may produce symptoms. A person with headaches due to food allergy may also have headache when his tolerance is lowered by constipation, emotional upsets, etc. When hay fever is complicated with sinus infection each of the two conditions tends to make the other worse.

This explains why relief is sometimes obtained in the treatment of primarily allergic diseases by means of non-allergic methods.

Experience has shown, however, that the most appropriate procedure consists in breaking the vicious circle by correcting the allergic state in so far as possible. When this does not provide satisfactory relief the other methods of approach (dermatologic, rhinologic, etc.) may be used to supplement it.

only a small part of allergy and the improvement is but temporary. Such patients usually tell the story of trying one remedy after another, finding that each helps for a time, but the good effects wear off.

Indeed, although he may be unconscious of the fact, the allergist himself helps the patient, in part, at least, with the same psychologic hocus-pocus. His approach to the patient's problem, his method of diagnostic study, and his optimistic assurance of relief go a long way toward fostering early improvement. But the doctor knows that this has never produced permanent cure, and organizes his programme for continuing treatment based upon the sounder principles of allergy.

Chapter XXVI

THE MAN WITH ALLERGY

IN OUR ENTHUSIASM FOR STUDY OF 'THE ALLERGY THAT HAS THE patient' we must not overlook the *patient who has the allergy*.

We may talk, with what appears to be great exactness, of the chemical reactions taking place, of physiologic and nerve responses to these reactions, of antigens, antibodies, and shock tissues, but we must remember that as far as man is concerned an allergic reaction cannot take place in the absence of a person for it to take place in. This person will assure the doctor that he is much more interested in his own sense of well-being than in what is happening in the struggle between adrenalin and acetylcholine.

It is one of the strange facts of allergy that no two patients react exactly alike. Some react to one group of allergens, others to other groups. In some, one or another shock tissue is responsive, while in others several tissues respond. Treatment must be individualized and may be quite different in different cases. A man who has migraine caused by several foods and also happens to have tuberculosis should be treated quite differently from another who has migraine due to foods but no other disease except obesity. One would have no hesitancy in materially restricting the diet of the latter, but this could not be done safely with the former. The same applies with many other non-allergic diseases which may afflict allergic persons. One must treat the man with his allergy, not merely his allergy.

Many factors besides allergenic excitants may influence symptoms. Some allergics are influenced by atmospheric conditions. Like the person with rheumatism, they can tell when the weather will change because their own symptoms are becoming better or worse. General dietary factors may play a part. Two doctors found that they could sensitize guinea pigs to a drug, arsphenamine,

in Boston, but that they could not do so with guinea pigs in New York. The suggestion was made that the difference in the type of food fed to the animals in the two laboratories might play a part. This might also bear on the fact that guinea pigs from the United States, Argentina, and France cannot be sensitized with equal ease, some resisting sensitization more than others. Recent animal investigations suggest that vitamin C deficiency may favour the absorption of allergenic foods even though the deficiency appears to have no influence on the original production of sensitization.

In the matter of guinea pigs from different parts of the world it is difficult to determine whether the food or some other environmental factor is the important thing, or whether it is a matter of race and breed. The same question remains unanswered with humans. The American Indian, in the same environment with, and possibly eating very much the same food as the white man, is less susceptible to hay fever. Malay and East Indian natives are less susceptible than whites living on the same plantation.

Primitive man learned from hardship and bitter experience that he must have certain foods in order to remain robust. Weston Price's recent study of the staple foods of those remnants of primitive peoples scattered over the seven seas is illuminating. He found that those tribes, whether they be Eskimos or Australian aborigines, South Sea Islanders or savages in the heart of Africa, which as yet have no commerce with the white man, have normally developed jaws and are free from tooth decay. All have learned the need for fresh vegetables, fruits or nuts, and some type of animal food or sea food. He tells of two warring factions on a small Pacific island. One held the uplands, while the other had the coast. Both groups knew that, to stay well, they must have both upland food and sea food. Although each would kill the other on sight, there was a tacit biologic agreement. Each evening those on the coast deposited sea food at an isolated cairn, for the use of the highlanders. The latter removed this, replacing it with the products of the forest. This having been done, they were again at war.

Dr. Price also tells of the Indians of Northern Canada who knew that a man with scurvy can cure himself by eating a small apple-shaped organ found at one end of the moose's kidney. We know to-day that this organ, the adrenal gland, is the richest animal source of the scurvy preventive, vitamin C.

Price presents evidence that our modern diet, with its white bread and canned goods, in the processing of which many important minerals and vitamins are lost, is responsible for certain types of physical deterioration. He found an interesting example on a small Pacific island. Ships stopped regularly only during the first World War, when the price of copra had advanced from $40 to $400 per ton. Copra was plentiful on the island. After the war there was no market, and the natives saw no ships. During

the boom they were paid in cloth and the white man's food. The natives had splendid teeth until the war. Then came tooth decay. Those born after the war again had excellent teeth.

Any possible application of these observations to allergy is pure conjecture. If allergy is increasing with the increasing artificiality of our existence, modern methods of food processing must be considered along with other possible factors. It would be interesting to follow in Dr. Price's footsteps, making a survey of the prevalence of allergy in the same primitive groups. I should not be surprised to find it a most unusual malady.

In any event, until more is known of this phase of the subject it behoves the person with allergy to maintain as broad a diet as possible, and it is especially important for the doctor, when placing his patient on dietary restrictions, to provide an adequate supply of vitamins and other food essentials.

Other Remedies

One who has read the story of allergy as it has been presented in this volume might infer that, as far as treatment is concerned, there are but two things to be done: to avoid the allergen if possible, or, this failing, to be desensitized against it. While these are the specific measures on which we must depend for the eradication or counteraction of the basic causative factors, many other non-specific remedies are in daily use. These drugs possess the advantage of giving quick relief from the acute attack; the disadvantage that, although they relieve the episodes of the moment, their beneficial effects are not permanent. The combined use of specific and non-specific remedies should give greater relief than either alone.

The most important symptomatic remedy is adrenalin. It is a logical remedy. It stimulates the sluggish sympathetic nervous system to more efficient activity. Unfortunately, the good effects of one injection last but a few hours.

A Chinese weed whose botanical name is *Ephedra vulgaris* produces a drug which is so nearly identical with adrenalin that it has practically the same effect on man. This medicine has been named ephedrine, after the plant from which it is obtained. It has one advantage over adrenalin, that it is active when taken by mouth, and need not be given hypodermically. It has its disadvantages. It is not as powerful and is not as effective in controlling severe allergic reactions. It takes longer to exert its effect, but when established this is usually of greater duration. Both adrenalin and ephedrine have their uses.

Some persons become allergic to ephedrine and can use it no longer. For them the chemists have come to the rescue. They have synthesized—that is, manufactured in the laboratory—chemical compounds which are almost identical with ephedrine.

There are several, each differing slightly from the other and from ephedrine. Consequently, one who is allergic to the latter may take one or other of the synthetic ephedrine-like compounds.

Morphine in large doses is a deadly poison. Those who take morphine for long periods develop tolerance to it, so that they can eventually take doses which would be fatal for one who has not acquired the habit. The same is true with histamine, the poison formed in the body which causes allergic symptoms. Fortunately, it does not cause 'habituation,' like morphine. Why not inject histamine repeatedly and in gradually increasing doses until the allergic patient has acquired an increased tolerance? If when this has been done the patient has an allergic reaction with automatic release of histamine, his body should be less responsive to the poison, and his consequent symptoms should be less severe.

When this idea was put to the test with animals it appeared to work according to theory. Histamine was injected into guinea pigs in increasing doses until the animal at last tolerated quantities which were uniformly fatal for other guinea pigs that had not received the preparatory injections. Others were sensitized to horse serum. Their tolerance to histamine was then increased by repeated injections. Finally, they were given second injections of serum, larger than the minimum lethal dose (page 74). These pigs should have died, but, although they became ill with anaphylactic shock, they recovered.

The same procedure applied to the treatment of allergy in man has not been as successful although some persons improve temporarily. Allergists are still investigating the possibilities of this treatment.

Histamine is a poison. Must one give injections of histamine to increase the ability to tolerate it? Isn't it possible that an antidote might be discovered which would destroy the action of histamine? Recently it appeared as though this had been done. A scientist discovered that when he injected an extract from the liver of the turkey buzzard along with histamine his guinea pigs did not have histamine shock, as they should have. Something in the extract had prevented the harmful action of histamine. This might be a ferment present in certain tissues which will destroy histamine. This hypothetical substance was named histaminase. Apparently it was also present in the kidneys of ordinary pigs and in other tissues. Histaminase has recently been used widely in the treatment of human allergy. The results have, on the whole, been disappointing. This, then, is another of the possibilities still under investigation.

Other drugs are used more or less routinely in the treatment of acute allergic episodes. They are such as atropine, which in a measure counteracts the activity of the parasympathetic nerves, iodides, calcium, glucose, hypnotics, caffeine, ergotamine, aminophylline or theophylline, and several other commonly known pre-

parations which are of value because they temporarily relieve one or another of the acute allergic symptoms.

Problems for the Future

Man and his allergy are a truly strange combination. Foods, drugs, and other substances which should in all reason be beneficial to everyone become dangerous poisons for some. It is not the allergen which is at fault, otherwise it would be equally poisonous for all. One man reacts differently from others (*allergy*) ; this reaction is peculiar to the individual (*idiosyncrasy*) ; it is indeed a strange disease (*atopy*).

Is allergy becoming more common? We do not know, but certainly it appears to be doing so. If it is, we would like to know why, in order that we may so alter our mode of living to counteract the tendency. The outlook for the future will be brighter if we can prove that the disease is becoming more common, because in this case there must be a cause, and after we have discovered the cause we should be able to do something about it. If, on the other hand, the disease has existed, unchanged, since earliest times, we must conclude that it is intrinsic in the processes of life and that there is little that we may do to prevent it or to remedy it.

I like to believe that it is becoming more widespread and that the increasing artificiality of our mode of living is an important factor in its causation. To-day, when sick we take drugs which never existed until a few years ago. We find that persons are especially prone to become sensitized to them. We inject the blood of horses into our veins and some become extremely ill. We take arsphenamine, sulphanilamide, aspirin, and many other chemicals prepared by the artifices of man, and some of us get into difficulties.

We live in air-conditioned homes, cooled in summer and heated in the winter, and when out of doors we protect ourselves in closed automobiles. Is it any wonder that some of us have lost the ability to adjust ourselves quickly and adequately to sudden changes in temperature?

The factory worker, whether he be making rubber products, dyes, paints, new metal alloys or any of a thousand other products, is working routinely with chemicals which were non-existent a few years ago.

There is quite convincing evidence that, at least with the minor allergic (the man who does not easily become sensitized), the newer and the more strange the substance with which he comes into contact, the more likely he will be to become sensitized against it. Each day many of us are handling, swallowing, or breathing one or another of these strange new articles.

The major allergic, the man who has the tendency so strongly that he will become sensitized even to old familiar substances such as wheat, milk, house dust or pollen, also becomes sensitized to

these new unusual excitants, and apparently to the same extent as the minor allergic.

Assuming that allergy is on the increase, is it purely a matter of failure to adjust oneself to new acquaintances? If this be true, all that we need is to return to the simple life. We might stop all progress at the stage where we find it to-day. Gradually we will adjust ourselves, and as we become accustomed to exposure to the things which have been new up until now we will experience less trouble from them.

I doubt if it is as simple as this. Is it possible that we have unconsciously discarded certain protective elements which formerly enabled us adequately to tolerate new exposures? The most obvious possibility along this line would be the loss of some protective food substance. To-day we talk much of vitamins. We are but commencing to learn the importance and absolute need for these infinitesimal food elements, so necessary to normal life. We have learned that the vitamins are indispensable for the cell, the unit of life whose proper activity is essential for the normal life of the body as a whole and one of whose abnormal reactions is allergy. The average diet to-day is more abundant, more adequate, and better balanced than at any previous time in the history of the human race in every respect except its vitamin content. Most of us secure ample fat, protein and carbohydrate, water, and probably minerals. But many of us are short on vitamins.

Our remote ancestors ate whole-wheat bread instead of bread made of white flour from which so many of the nutritious elements have been removed. White bread is still a good food provided one supplies the missing elements in other articles of the diet. But bread as we eat it to-day is no longer the staff of life, and one who depends upon it more or less exclusively as a source of food will soon become ill.

Man discovered early in his existence that for normal health he must reinforce the products of the field with animal food or food taken from the seas. The savages found from experience that animal-organ foods, such as liver, sweetbreads and kidney, are more nutritious than muscle foods, even though the latter may taste far better. Unconsciously, they selected those foods which are rich in cellular material and consequently rich in vitamins or possibly in other yet undiscovered elements which promote normal cellular activity.

To-day, with the exception of meats and fresh fruit, we eat predominantly preserved foods coming chiefly out of cans. Many of the vitamins are soluble in water, and some are destroyed by heat. When we eat canned beans the cook has thrown away important vitamins and minerals along with the water in the tin. We get the taste of beans and most of the protein, sugar, starch, and fat, but we have discarded two important elements. In olden times this

was not done. When the kitchen range had a wood fire the soup pan simmered at the back and the liquor from boiled vegetables was not wasted, but was poured into the pan. To-day, with gas ranges and electric stoves, we can do this no longer, because the heat is there only when needed for cooking, and the old soup pan would now cool down intermittently, becoming the finest of culture media for bacteria.

I do not mean that deficiency in vitamins is the cause of allergy. There has been nothing to indicate this. There is evidence that deficiency in vitamin C may promote absorption of incompletely digested foods and might, therefore, favour an allergic reaction in a person already sensitized. There is no evidence as yet that deficiency actually causes the original sensitization. All that we may say at present is that until we know more of the ultimate importance of vitamins a logical precaution for the person with allergy will be to make sure that he has no vitamin deficiency. His doctor can now do this by testing for some of the vitamins, and undoubtedly will soon be able to do so for many more. Fortunately for the allergic patient who must avoid many foods, purified or synthetic vitamins may now be taken like medicine.

We can easily understand that ragweed and other weeds cause so much pollinosis, because our careless horticultural methods promote increasing weed growth. But this does not explain why so many persons become allergic to their pollens.

What of the hereditary factor? If allergy is on the increase, is it because we are cross-breeding a race of persons among whom the allergic predisposition is more or less dominant? Here, again, we do not as yet know the answer. Evidence at present indicates that major-allergic mates are more than likely to have allergic children. But would this justify one in recommending that two such people, in love and otherwise adapted to one another, should not marry? Not in the present state of our knowledge.

The study of allergy is one of the most fascinating fields of medical investigation. It is the study of one of the processes of life itself. It is the study of the vital activity of the living cell, the unit of life. Bacteria may grow in a dead body, but without life, without cellular activity, there is no allergy. When at some future time the riddle of allergy has been solved it will be a long step toward the solution of the riddle of life itself.

Allergy is equally fascinating and ofttimes most baffling to the non-medical public. There is scarcely a family in the United States into which the malady does not intrude at one time or another. There is rarely an aggregation of one hundred, one thousand, or ten thousand in which half of those present have not suffered from, or will not experience, some manifestation of the disease.

Until within the last quarter-century little could be done to help them. To-day, although the underlying tendency cannot be

removed, the majority of such persons can secure varying measures of relief, even up to entire disappearance of symptoms. The purchase price is often high, involving strict dietary taboos, which may include those foods which the victim has loved above all others, and desensitizing injections which become monotonously long continued, and are tolerated only because one realizes that symptoms will return if they are stopped.

Medical science has reached the stage at which it can explain to the patient with allergy what is the matter with him. It can provide the needed remedies. It has not yet discovered the cure, the treatment which will prevent persons becoming sensitized in the first place ; nor will this be accomplished until after we have learned more of the mechanism of life itself, until, as the saying goes, we have found what makes the wheels go round. The progress of science during the past one hundred and fifty years has been nearly as great as that in all the centuries which have preceded it, from man's earliest days. During the past thirty years students of allergy have discovered nearly all that need be learned except the final key. To-day, we can give a clear and probably fairly accurate explanation of *how* allergy works, but there are still gaps in our understanding of the *why*.

Like to-morrow's sun the answer will come. We do not know how soon. It may be next year. It may be a decade or a century from now. The time may come when the paraphernalia of skin testing and kindred methods of study will be discarded, and when one who is allergic, to no matter what, need only take some pill or other alternative remedy which will relieve him of his discomfort. Until that time the man with allergy must continue to adjust himself to those environmental influences which happen to be harmful to him, in accordance with the precepts which have been herein recorded.

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My acknowledgments would not be complete without mention of the painstaking and often brilliant investigations of the host of scientists, immunologists and allergists, which have made it possible for us to understand so clearly, to-day, what is probably taking place in the allergic reaction. In this book I have stated that while the Ehrlich side-chain theory is no longer adequate, it is still used even in medical school instruction because (1) it lends itself to graphic presentation, and (2) it still remains the basic concept on which more recent knowledge of the nature and action of antibodies is built.

It has been said that we know antibodies, not by what they are, but by what they do. Nobody has ever seen an antibody. Investigations of the last few years require modification of this statement. We know, to-day, that antibodies are blood globulins (protein) ; we know their molecular weights (differing in different species of animals) ; we know in general how they are formed (by unrolling of the protein molecule and a templating, complementary to the antigen—but this is too complicated for a book designed to make it easy for the reader) ; we know approximately which cells in the body manufacture the antibodies and we can almost say that we have seen antibodies, since we have actually seen their shadows (about 30 angstrom units broad by 300 units wide), as projected in the electron microscope.

RICHMOND, VIRGINIA.
January 1, 1941.

INDEX

Q

R

S

T

U

V

W

Y